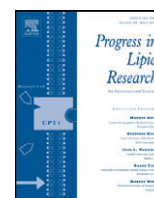




Contents lists available at ScienceDirect

Progress in Lipid Research

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

Review

Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults

Ken D. Stark^{a,*}, Mary E. Van Elswyk^b, M. Roberta Higgins^c, Charli A. Weatherford^d, Norman Salem Jr.^e^a University of Waterloo, Department of Kinesiology, 200 University Avenue, Waterloo, ON, N2L 3G1, Canada^b Scientific Affairs, Van Elswyk Consulting, Inc., 10350 Macedonia St., Longmont, CO 80503, USA^c MEDetect Clinical Information Associates, Inc., PO Box 152, Skippack, PA 19474, USA^d Weatherford Consulting Services, Poteet, TX, USA^e DSM Nutritional Products Ltd., 6480 Dobbin Road, Columbia, MD 21045, USA

ARTICLE INFO

Article history:

Received 18 December 2015

Received in revised form 14 May 2016

Accepted 18 May 2016

Available online 20 May 2016

ABSTRACT

Studies reporting blood levels of the omega-3 polyunsaturated fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), were systematically identified in order to create a global map identifying countries and regions with different blood levels. Included studies were those of healthy adults, published in 1980 or later. A total of 298 studies met all inclusion criteria. Studies reported fatty acids in various blood fractions including plasma total lipids (33%), plasma phospholipid (32%), erythrocytes (32%) and whole blood (3.0%). Fatty acid data from each blood fraction were converted to relative weight percentages (wt.%) and then assigned to one of four discrete ranges (high, moderate, low, very low) corresponding to wt.% EPA + DHA in erythrocyte equivalents. Regions with high EPA + DHA blood levels (>8%) included the Sea of Japan, Scandinavia, and areas with indigenous populations or populations not fully adapted to Westernized food habits. Very low blood levels (≤4%) were observed in North America, Central and South America, Europe, the Middle East, Southeast Asia, and Africa. The present review reveals considerable variability in blood levels of EPA + DHA and the very low to low range of blood EPA + DHA for most of the world may increase global risk for chronic disease.

© 2016 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1.	Introduction	133
2.	Systematic review methodology	133
2.1.	Search strategy	133
2.2.	Inclusion exclusion criteria	133
2.3.	Search results screening and data extraction	133
2.4.	Search results	133
3.	Converting fatty composition data to similar units for comparison	134
3.1.	Converting fatty acid data to relative weight percentages	134
3.2.	Converting blood levels of EPA + DHA to erythrocyte based ranking	134
4.	Results	135
4.1.	Included study characteristics	135
4.2.	Global distribution of EPA + DHA in human blood	135
4.3.	Global distribution of individual n-3 LCPUFA	137
5.	Discussion	137
5.1.	Countries with limited, excluded or no data	139
5.2.	Units for expressing fatty acid compositional data	139
5.3.	Diet and blood	142
5.4.	Potential consequences of low blood levels of EPA + DHA	143
5.5.	The challenge of increasing blood EPA + DHA levels through dietary intakes	144

* Corresponding author at: Department of Kinesiology, University of Waterloo, 200 University Avenue West, Waterloo, Ontario N2L 3G1, Canada.

E-mail addresses: kstark@uwaterloo.ca (K.D. Stark), mveconsulting@q.com (M.E. Van Elswyk), medetect@aol.com (M.R. Higgins), charliaweatherford@gmail.com (C.A. Weatherford), Norman.Salem@dsm.com (N. Salem).

6. Concluding remarks	145
Conflicts of interest	145
Acknowledgments	145
References	145

1. Introduction

Noncommunicable disease or “chronic disease” mortality is estimated to be the cause of death for 38 million people worldwide each year, disproportionately effecting those in low and middle-income countries and unhealthy diets are considered a main contributor [1]. Determining global variation in nutrient status informs the process of creating national and worldwide dietary guidance. Dietary omega-3 long-chain polyunsaturated fatty acids (LCPUFA), eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), have been associated with a decreased risk of chronic disease, in particular cardiovascular mortality [2] and cognitive decline [3]. Global dietary intakes of omega-3 LCPUFA has been examined and it has been estimated that less than 20% of the world population consumes ≥ 250 mg/day of seafood omega-3 polyunsaturated fatty acids (PUFA) [4]. However, the reliability of EPA + DHA intake estimates is limited by various factors including the availability of accurate and timely food composition data in nutrient databases that can differ across countries [4,5] but also the challenge of reporting errors in the collection of dietary data [6,7]. The fatty acid composition of blood does not have these limitations and blood EPA + DHA also reflects other metabolic factors and behavioral choices that can influence EPA + DHA status [8–12]. Blood levels of omega-3 PUFA, particularly EPA and DHA have been linked to a reduced risk of primary cardiac arrest [13], sudden cardiac death [14] and all-cause dementia [15]. Therefore, our objective was to systematically review the available literature and identify studies reporting blood EPA + DHA levels to create a visualization of global EPA + DHA status useful for identifying countries and regions potentially at an increased risk of chronic disease due, at least in part, to their omega-3 LCPUFA status. The results of the global map of blood levels of EPA + DHA and blood level recommendations are contrasted against reports of dietary intakes and dietary intake recommendations. In addition, the possible consequences of global blood levels on chronic disease risk and the challenges of achieving blood levels recommended to reduce chronic disease risk are discussed.

2. Systematic review methodology

2.1. Search strategy

To identify relevant studies, a comprehensive literature search was conducted using two scientific literature databases (PubMed and Embase) through April 2014. Supplementary literature searches included examining the reference lists of all relevant studies, pertinent review articles, and meta-analyses. Included studies published after the date of literature search were identified via publication alerts. Relevant terms representing EPA and DHA and blood fatty acid measurement were used for each database searched. When appropriate, subject headings were exploded and terms truncated (see PubMed search strategy in Supplementary Table S1).

2.2. Inclusion exclusion criteria

Included studies were those of healthy adults (≥ 16 years) reporting, at a minimum, red blood cell, plasma, or whole blood of both EPA and DHA fatty acid data, published in 1980 or later, and using a capillary column to separate fatty acids. Studies of pregnant and nursing women, infants and children or subjects with existing disease were excluded.

Studies of individuals with disease risk factors were included. All study designs were eligible with the exception of individual case studies. Preference was given to studies published in English, however, studies in other languages were considered if data was otherwise unavailable for a particular country. When data from randomized, controlled trials was used only baseline data from subjects in the placebo group was included.

2.3. Search results screening and data extraction

Level I screening of search results included a review of all titles and/or abstracts compared to eligibility criteria. Full-text publications of any studies not eliminated at Level I were retrieved for complete review at Level II screening. All search results were screened by two individuals with approximately 95% agreement regarding included and excluded studies. Differences were resolved by discussion and consultation with a third researcher as needed. Two researchers completed data extraction for all studies, one review author checked text entries, and one independent quality control person checked numeric outcome data. Included studies were further examined to identify related or “kin” studies. When kin studies were identified, the study reporting the most detailed fatty acid data for the largest sample size was selected for further data extraction and the other kin publications were excluded. All included studies provided at minimum, individual data for EPA and DHA and, if available, data for 14:0, 16:0, 18:0, 20:0, 22:0, 24:0, 16:1n-7, 18:1n-7, 18:1n-9, 20:1n-9, 22:1n-9, 24:1n-9, 18:2n-6, 18:3n-6, 20:2n-6, 20:3n-6, 20:4n-6, 22:4n-6, 22:5n-6, 18:3n-3, 20:5n-3, 22:5n-3, and 22:6n-3 was also collected for further evaluation.

Age range was an extracted variable of interest that was not consistently reported in all studies. Some studies, for example, reported age only as > 18 or as a population mean age. If an age range of the study participants was not presented, the upper and lower limits of the age range were calculated from the standard deviation by adding and subtracting 2 times the standard deviation from the mean age (2SD method). Standard deviations were calculated as needed. In some instances, generally in studies with samples sizes less than 100 subjects ($n = 15$), the range generated from 2SD method was inconsistent with recruited (e.g. age consistent with young children in study of adults) or was an implausible range – i.e. a negative age for the lower bound. In these instances, the standard error of the mean was multiplied by the appropriate critical z value and added and subtracted from the mean to determine 99.99% confidence intervals that were used to establish the age range.

To ensure data integrity the spreadsheet containing all extracted data was quality checked, assigned a version code and maintained apart from the live/working spreadsheet to prevent any further changes. If the live/working spreadsheet required modification in a manner that would impact analytical outcomes the previously “locked” spreadsheet was modified accordingly, assigned a new version code, and then maintained as the “locked” dataset. The final locked dataset, used for outcome summaries, was the third dataset in a series.

2.4. Search results

The original search yielded 877 references, supplemental searching resulted in identification of an additional 47 references, of these 585 were excluded based on initial (Level I) screening of abstracts and/or titles (Fig. 1). The most common reasons for exclusion of studies at Level I screening were participants with existing disease (38% of excludes)

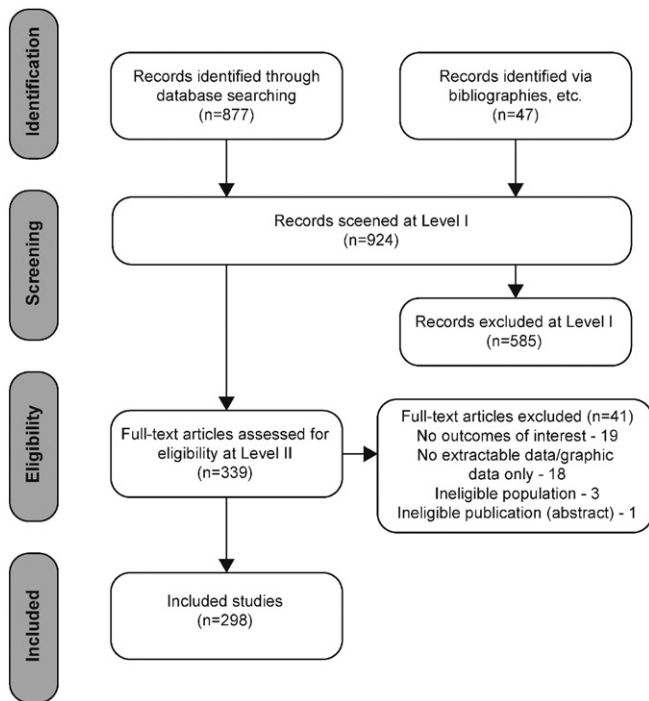


Fig. 1. Flow diagram of inclusion/exclusion process.

followed by studies that had no outcomes of interest or a lack of data on individual fatty acids (29%). In addition, there were several studies excluded as the participants were pregnant/lactating (16%), children (2.2%) or “other” (institutionalized, selected for low fish intakes, etc.) populations (2.3%). Other exclusions included relationship to an existing kin study already in the database (4.5%), inappropriate publication type (e.g. abstract) (4.3%), or irrelevant/unrelated studies (3.7%). Full-text publications of 339 studies were retrieved for complete review at Level II. At Level II, most studies were excluded for providing only graphical data or not providing results for a blood fraction of interest (Fig. 1). Although some studies had multiple reasons for exclusion, each study was classified into only one exclusion category. A total of 298 studies were included [5,6,14,16–310] and a total of 626 studies were excluded (Supplementary Table S2).

3. Converting fatty composition data to similar units for comparison

3.1. Converting fatty acid data to relative weight percentages

Extracted data was sorted into categories of blood fraction analyzed and included plasma total lipids, plasma phospholipid, erythrocytes and whole blood. Serum data was included in the appropriate plasma categories and erythrocyte phospholipid data was included in the erythrocyte category based on previous findings that the fatty acid composition of plasma and serum [311] and of erythrocyte total lipid and erythrocyte phospholipids [312] are similar, respectively. Within a blood fraction, studies were also sorted according to the units used to express the data. The units used fell into categories of relative quantification (the weight or mole percentage of an individual fatty acid relative to the total fatty acids) and absolute concentration (the concentration of a fatty acid in a volume or mass of the blood fraction). The most common method of data expression was as the weight percentage of total fatty acids (78% of the extracted data) while expression as mole percent accounted for only 5% of the extracted data. Fatty acid weights expressed in a blood fraction volume was the most common method of expressing concentrations and accounted for 12% of the extracted data with the units, μg of fatty acid/mL of blood being used most

commonly. Mole based concentrations accounted for only 5% of the data extracted. Within blood fractions, the fatty acid composition of plasma phospholipids, erythrocytes and whole blood were presented mainly as relative percentages (92, 98 and 92%, respectively) while for plasma total lipids the use of relative percentages was slightly lower (62%) as the use of concentration units (mole and weight based) was slightly more common (38% of data from this blood pool).

In order to facilitate comparisons, data was converted to relative weight percentages within each blood fraction. This approach was employed based on the fact that most of the data was already expressed in this format and could not be converted to concentration data due to the lack of quantitative information on fatty acid and blood fraction volume reported in the original publications. Concentration data that indicated either the concentration of the sum of total fatty acids; the sums of saturates, monounsaturates and polyunsaturates; or a comprehensive list of the concentration of individual fatty acids were readily converted to relative percentage data. Data expressed as mole concentrations was converted to mass units using the molecular weight of individual fatty acids and then converted into relative weight percentages. Fatty acid compositions presented as mole percentages were converted by dividing the mole percentage of an individual fatty acid by 100 and then multiplying by the respective fatty acid molecular weight to express the data as g of individual fatty acids over the total sum of fatty acids in moles. The individual fatty acids were summed to determine the total sum of fatty acids in g over the total sum of fatty acids in moles. The mass of each individual fatty acid over total sum of fatty acids in moles was then divided by the mass of the total sum of fatty acids over the moles of the total sum of fatty acid and multiplied by 100 to convert the fatty acid composition to weight percentages. This conversion method required comprehensive fatty acid profiles to complete. Approximately 12% of the data extracted was converted (47/398 lines of extracted data within our spreadsheet) to relative weight percentages and 6.5% of the data could not be converted (26/398 lines of extracted data) due to the inability to determine the sum of total fatty acids (usually no saturated and monounsaturated fatty acids reported). Data not converted to relative weight percentages was not included in the development of the global map of the sum of the percentages of EPA + DHA, but this data is included in the summary tables.

3.2. Converting blood levels of EPA + DHA to erythrocyte based ranking

In order to compare the omega-3 PUFA status across the globe, EPA + DHA in erythrocytes was selected over other omega-3 PUFA blood biomarkers [311], as it has been well defined in the literature previously [313]. Therefore, it was necessary to convert the fatty acid composition data from different blood fractions to EPA + DHA equivalents to generate a single, comprehensive global map. If EPA + DHA as a specific sum was not presented in the original publication, it was calculated by summing reports of 20:5n-3 and 22:6n-3 and added to the database. The amount of data extracted from the literature was relatively equal from plasma total lipid (33%), plasma phospholipids (32%) and erythrocytes (32%) while data from whole blood (3%) was relatively limited. Within each blood fraction, data from each study was weighted by study sample size, summed with studies from the same country and dividing by the sum of study sample sizes for that country. In order to combine data from different blood fractions for each country, previously published modeling and translation methods were applied [314]. These methods indicate that converting continuous EPA + DHA in one blood fraction to continuous data in another blood fraction is possible, but that the degree of concordance is greater when discrete categories are used for translation. Therefore, the categories used in this translation study were derived from levels of EPA + DHA in erythrocytes associated with high to low risk of death from coronary heart disease that were presented when the “omega-3 index” was introduced [313]. The continuous data was assigned to one of four discrete blood level groupings that corresponded to EPA + DHA weight percentage values in

erythrocytes of ≤ 4 (very low), $>4-6$ (low), $>6-8$ (moderate), >8 (high). Equivalent groupings for plasma total lipids [≤ 2.9 (very low), $>2.9-4.0$ (low), $>4.0-5.2$ (moderate), >5.2 (high)], plasma phospholipids [≤ 3.8 (very low), $>3.8-5.7$ (low), $>5.7-7.6$ (moderate), >7.6 (high)] and whole blood [≤ 3.0 (very low), $>3.0-4.4$ (low), $>4.4-5.9$ (moderate), >5.9 (high)] were determined according to equations as described previously [314]. Each grouping was assigned a categorical score (1 – very low through 4 – high). The categorical scores for different blood fractions were weighted by total number of participants for each blood fraction and summed with the weighted values of other blood fractions for each country. The sum of the weighted score values were then divided by the sum of the samples sizes and rounded to the nearest whole number (1 – very low, 2 – low, 3 – moderate, 4 – high) to determine the discrete category to represent the country. Data for individual studies within a country were also ranked and compared to the blood level category of their representative country as a check for potential regional differences within a country. Large differences were observed between the overall country rank with studies examining indigenous populations in Alaska (versus United States of America), Northern Canada (versus Canada), a fishing region of South Africa (versus Cape Town) and Northern Russia (versus Central Russia), as well as the Primorsky Krai region of Russia (located on the Sea of Japan). These regions were removed from country data and categorized to their own distinct region. The country blood level categories were assigned colors (very low – red, low – orange, moderate – yellow, high – green, no data – gray) that were used to generate a global heat map for blood levels of EPA + DHA using a royalty-free vector map of the world image purchased from Adobe Stock (Adobe Systems Incorporated, San Jose, CA USA) that was modified using Adobe Illustrator CS6 ver. 16.03 (Adobe Systems Incorporated).

4. Results

4.1. Included study characteristics

The main characteristics of the included studies are summarized in Table 1. Epidemiologic observational studies provided the majority of data points. The majority of studies enrolled subjects 20 years or older with slightly more males than females. Plasma total lipid fatty acid composition totaled 131 lines of extracted data, representing 36, countries/distinct regions with the USA having the most data reported with 27 lines followed by Japan with 20 data lines (Table 2). Plasma

phospholipid based data lines totaled 127 lines of data overall, with 31 countries/regions represented (Table 3). The USA had the most lines of data reported at 18 followed by Canada with 14 lines of data. For erythrocyte data, there were 128 lines of data, representing 33 countries/distinct regions (Table 4). China had 29 data lines, but 24 of these data lines came from a single study [126] that examined the various provinces and municipalities across China. The USA had 17 lines of data for erythrocytes. Whole blood data was limited to 12 lines of data that represented 4 countries with 5 lines of data from the USA and 4 from Canada (Table 5).

Overall, data from 54 countries/distinct regions were identified but the amount of data for a specific country varied widely. Studies conducted in North America contributed the most data points ($n = 114$ lines of extracted data) followed by Asia ($n = 96$), Scandinavia ($n = 73$) and countries within Europe ($n = 71$). In contrast, data from Central and South America and Africa was limited. The USA had 67 lines of data in total, which was by far the most data for a single country. Japan, China and Canada had 32–35 lines of data, while Italy, France, the UK, Australia, Norway, the Netherlands, Finland and Sweden had 10–20 lines of data. It is concerning that for almost half of the countries/regions ($n = 26$), there were only 2 (10 countries/regions) or 1 (16 countries/regions) lines of data. When the data was examined according to samples size of the studies, Japan had the largest amount of individuals examined ($n = 26,877$) followed by the USA ($n = 22,700$). China, the UK, Finland, France, Italy and Australia were countries with data collected from more than 5000 individuals. Again, data from almost half of the countries was based on limited data as 27 of the countries had data that represented less than 300 individuals with 14 countries having data from less than 100 individuals. There was an interesting pattern where “normative” data for some countries was exceeded by data for distinct populations. Sampling from Russia was particularly uneven with a large study sample from the Primorsky Krai region on the Sea of Japan ($n = 1174$) and study samples on indigenous people living in the north ($n = 131$ in total), while we could only recover limited data for central Russia ($n = 113$). In South Africa, a fishing population in St. Helena Bay ($n = 25$ subjects) was compared to urban Cape Town inhabitants ($n = 25$ subjects) [250]. The focus on distinct populations was also observed in data from Canada as the number of individuals examined in a distinct Cree/Inuit region ($n = 5087$) was greater than the number of individuals examined for the country as a whole ($n = 4104$). The only other example was studies examining the Alaskan Yupik ($n = 1573$ subjects), but the number of total subjects representing the general population of the USA was much larger ($n = 22,700$).

4.2. Global distribution of EPA + DHA in human blood

Detailed fatty acid composition data for plasma total lipids, plasma phospholipids, erythrocytes and whole blood extracted from the included studies is presented by country within continental regions (Tables 2–5). The data are presented as relative weight percentages whenever possible with data that could not be converted included at the end of each country list. The number of individual fatty acids reported in addition to EPA and DHA was variable across the studies. Values for 20:0, 22:0, 24:0, 18:1n-7, 20:1n-9, 22:1n-9, 24:1n-9, and 20:2n-6 were presented for less than 20% of the included data which is somewhat understandable given that they make up a relatively small percentage of the total fatty acid composition. However, fatty acids that make up a considerable percentage were also reported inconsistently, with 16:0, 18:0 and 18:1n-9 being reported for only 55% of the included data while 18:2n-6 and 20:4n-6 values were reported for 74% and 79% of the studies, respectively. The other n-6 polyunsaturated fatty acids were also poorly reported, with 18:3n-6 at 25%, 22:4n-6 at 31%, and 22:5n-6 at 23% of the total included data lines.

By rank assigning blood levels of EPA + DHA for each country and assigning colors for very low (red), low (orange), moderate (yellow)

Table 1
Demographics of included studies.

Characteristic	Percentage of studies
Age inclusion criteria (years of age)	
≥ 18	17.0
≥ 19	3.0
≥ 20	31.0
≥ 30	17.5
≥ 40	17.0
≥ 50	3.4
≥ 60	7.7
“Adult”*	3.4
Sex	
Female	47
Male	53
Study type	
Prospective cohorts and case-control studies	70
Randomized trials	30
Blood fraction	
Plasma total lipid	33.0
Plasma phospholipid	32.0
Erythrocyte	32.0
Whole blood	3.0

* The authors defined study age range as “adult” but included teenaged subjects < 18 years.

and high (green) blood levels, distinctive global patterns can be observed (Fig. 2). Regions with high blood levels of EPA + DHA were found in distinct regions with countries on the Sea of Japan (Japan,

South Korea, and Primorsky Krai region of Russia), Scandinavia (Denmark, Norway, and Greenland) and regions with indigenous populations or populations that are not fully adapted to industrial based or

Table 2
Global fatty acid compositions of plasma total lipids expressed as relative percentages.¹

Author (Year)	Ref	Country	n	14:0	16:0	18:0	20:0	22:0	24:0	16:1 n-7	18:1 n-7	18:1 n-9	20:1 n-9	22:1 n-9	24:1 n-9	18:2 n-6	18:3 n-6	20:2 n-6	20:3 n-6	20:4 n-6	22:4 n-6	22:5 n-6	18:3 n-3	20:5 n-3	22:5 n-3	22:6 n-3	EPA+DHA	
Asia																												
Chien (2011)	[49]	China	986																									
Zhang (2010) ²	[302]	China	92									703				1567			54	245			30	59	25	152	210	
Kibayashi (2000) ²	[135]	China	75																				21	40	61			
Lee (2000)	[155]	Hong Kong	133	0.50	17.80	13.00				1.00		18.80				29.50	0.50	0.20	1.10	6.30	0.40	0.20	0.80	1.30		3.40	4.70	
Abraham (2013)	[16]	India	50	1.76	32.19	11.90				2.17		21.03				19.93	0.54			5.27			0.37	0.45		0.68	1.13	
Mehendale (2009)	[186]	India	26	0.74	20.28	7.85						15.58		0.42		36.00	0.50		1.30	7.76		0.63	0.53	0.41		0.96	1.37	
Hirai (2000) ³	[108]	Japan	62	1.55	22.34	5.56				3.75		19.11				37.70				5.05			1.57	1.38		2.21	3.60	
Itakura (2011) ³	[119]	Japan	16397	1.08	23.76	7.24				2.95		21.89				26.49	0.48		1.11	5.15			0.64	3.02	0.79	5.37	8.39	
Ito (1999) ³	[120]	Japan	108		26.38	8.79						21.10			1.30	24.60				1.20	5.83		0.89	4.31		5.61	9.92	
Kuriki (2003)	[144]	Japan	94	0.83	23.08	7.71				2.23		18.94				31.61				6.17			0.79	2.32	0.59	4.51	6.83	
Kuroki (1997)	[147]	Japan	18	0.72	19.48	6.69	0.17	0.44	0.28	2.22		21.05	0.15		0.77	32.63	0.25			1.06	6.62		0.68	2.17		4.06	6.23	
Motoyama (2009)	[194]	Japan	285									26.40				26.40				6.60			2.60	0.90	6.00	8.60		
Nakamura (1995)	[201]	Japan	110	0.70	25.10	8.90				3.70		21.60				21.20			1.00	5.70			0.80	3.40	0.90	7.50	10.90	
Nogi (2007) ⁴	[206]	Japan	411		22.75	7.91						18.92				32.08				6.51			0.60	3.28	1.06	6.91	10.18	
Oda (2005)	[210]	Japan	42	0.89	23.22	7.24	0.24	0.59	2.96	2.11		18.98	0.07	1.20	27.47	0.21	0.19	0.99	2.99	0.11		0.88	3.45	0.78	5.52	3.97		
Sekikawa (2008)	[251]	Japan	281									26.80				26.80				6.60			0.20	2.50		0.90	8.40	
Takita (1996)	[273]	Japan	394		24.30	7.30				3.40		21.60				29.50				4.50			1.90			3.40	5.30	
Umemura (2005)	[281]	Japan	421	0.88	19.70	6.70				2.80		20.70				34.80	0.30		0.98			1.06	1.62	0.44	3.28	4.90		
Wakai (2005)	[290]	Japan	1257									26.80				29.50				4.50			2.64	0.82	5.00	7.64		
Yamada (2000)	[296]	Japan	261							2.70		29.90				29.90				5.90			0.63	3.80	1.34	8.40	12.20	
Yamada (2000)	[296]	Japan	202							2.50		21.10				21.10				5.30			0.71	3.20	1.20	7.70	10.90	
Ikeya (2013) ²	[117]	Japan	65																	167			99			155	253	
Kibayashi (2000) ²	[135]	Japan	25																				48			114	162	
Kitayama (2011) ²	[137]	Japan	1656																							138		
Konagai (2013) ²	[140]	Japan	42																							191	301	
Kondo (2010) ²	[141]	Japan	17																							116	182	
Tomiyama (2011) ²	[278]	Japan	2206													750	7			25	143		110			191	301	
Nogi (2007) ⁴	[206]	Mongolia	252		22.41	8.36						22.16				33.55				6.54			0.70	1.10	1.30	3.88	4.98	
Rezvukhin (1996)	[234]	Russia	28	2.24	21.56	9.49	0.71	2.23		2.98		29.56	0.53	1.18		33.76			0.94	1.61	3.73		1.04	0.00	0.47	1.97	1.97	
Rezvukhin (1996)	[234]	Russia-IN	18	4.39	29.69	13.27	0.62	1.33		3.06		21.70	0.32	0.22		17.25			0.42	0.79	4.31		0.18	0.94	0.38	3.39	4.33	
Rode (1995)	[239]	Russia-IN	41									27.74				27.74				0.90	7.43		0.55	2.73	1.79	4.13	6.86	
Manav (2004)	[178]	Singapore	145													4.83				4.50			0.47	0.33		3.07	3.40	
Manav (2004)	[178]	Singapore	147													4.50				4.50			0.57	0.30		3.53	3.83	
Nogi (2007) ⁴	[206]	S. Korea	418		21.82	6.82						19.60				36.11				6.75			0.60	2.19	0.71	5.40	7.60	
Sekikawa (2012)	[252]	S. Korea	301													24.70				6.02			1.97	0.81	4.83	6.83		
Oceania																												
Munro (2012)	[198]	Australia	28																				0.95			2.06	3.01	
Sullivan (2006)	[267]	Australia	53																				0.84	0.48		2.02	2.86	
van der Pols (2011) ²	[286]	Australia	147													242				124		2	11			39	49	
Rao (1996)	[230]	PNG	14	1.77	22.96	8.50	0.30	0.66		2.53		21.17				18.40		1.56		5.24	0.54	0.69	0.53	2.30		4.14	6.45	
Middle East																												
Alshatwi (2007) ²	[119]	S. Arabia	57													363				68		34	42		98	140		
Yerlikaya (2011) ²	[299]	Turkey	45	0.74	15.74	5.04	0.71	0.48	0.27	0.87		6.77	0.71	0.40	0.35	32.34		5.34		7.32		1.23	1.01		1.79	2.80		
Europe																												
Astorg (2008)	[26]	France	533													34.28	0.52	0.22	1.52	7.97	0.20		0.51	1.32	0.54	2.57	3.89	
Féart (2008)	[77]	France	1273	1.24	28.14	11.51				2.34		20.43				24.89	0.40			6.77			0.41	1.01	0.46	2.38	3.39	
Merle (2013)	[187]	France	605																			0.41	1.00	0.48	2.50	3.50		
Samieri (2008)	[246]	France	1149	1.24	28.14	11.58				2.32		20.34				24.90	0.41			6.75			0.41	1.03	0.47	2.41	3.44	
Samieri (2011)	[247]	France	1228																				1.01			2.39	3.40	
Samieri (2012)	[248]	France	281																				1.10			2.40	3.50	
Dawczynski (2010)	[61]	Germany	40													23.59				4.94			0.29	0.81	0.36	1.40	2.21	
Geppert (2008)	[84]	Germany	39														0.36			6.87						1.96		
Kalogeropoulos (2010)	[128]	Greece	374		20.40	6.70						19.00				26.40				5.18			0.25	0.36	0.32	1.56	1.92	
Panagiotakos (2010)	[213]	Greece	640													28.00				5.90			0.29	0.47	0.38	1.80	2.27	
McAfee (2011)	[183]	Ireland	38	1.13	25.66	6.79										27.42				7.57			1.33	0.82	1.01	1.05	1.87	
Cherubini (2007)	[48]	Italy	725		22.50	6.50						26.20				24.50				8.00			0.40	0.59		2.28	2.87	
Ferrucci (2006)	[79]	Italy	1123													24.92				8.08			0.46	0.64		2.30	2.94	
Lauretani (2007) ³	[152]	Italy	1241													25.26				8.19			0.47	0.47		2.35	2.	

Table 2(continued)

Africa																											
Yeh (1996) ³	[298]	Nigeria	397	0.99	29.37	7.32				2.11	23.51	24.87	0.26	1.17	4.74	0.25	1.80	3.62	5.42								
Schloss (1997)	[250]	SHB-SA	25	0.44	22.12	8.03				1.61	20.50	29.72		0.85	5.78	0.31	0.41	3.93	0.50	5.56	9.49						
Schloss (1997)	[250]	S. Africa	25	0.72	22.24	7.85				1.91	20.80	33.50		1.52	6.10	0.71	0.35	0.66	0.29	2.97	3.63						
Pauletto (1996)	[219]	Tanzania	53		27.10	8.30					22.60	15.00		1.15	9.70		0.60	0.30	2.30	1.10	5.70	8.00					
Pauletto (1996)	[219]	Tanzania	53		25.60	7.70					23.40	23.90		1.74	8.30		0.30	0.60	0.70	0.60	1.50	2.20					
Barkia (2011) ³	[32]	Tunisia	25	0.65	22.95	6.85	0.15	0.89	0.89	1.29	1.46	19.41	0.25	32.54				0.67				6.30					
Sfar (2010)	[253]	Tunisia	200		18.87	5.17					17.88	39.23		0.13	0.07	5.41		0.67				6.30					
																		0.79	0.95			3.10	4.05				
North America																											
Rode (1995)	[239]	CAN-CI	145									21.62		0.90	4.17		0.44	5.24	1.44	3.65	8.89						
Dodin (2008)	[71]	Canada	175	1.07	23.41	6.58				2.66	2.09	23.39		30.18		5.02	0.60	0.79	0.36	1.10	1.89						
Fortier (2010)	[81]	Canada	51	1.00	23.60	7.60				2.30	1.80	22.30		29.80		1.50	0.80	0.70	0.40	1.50	2.20						
Metherel (2009)	[190]	Canada	16	1.03	22.69	6.32	0.12	0.31	0.26	2.58	2.02	20.80	0.18	0.43	28.17	0.31	1.47	5.83	0.20	0.18	0.56	0.34	0.36	1.20	1.54		
Metherel (2012)	[191]	Canada	8	1.00	20.95	7.29	0.17	0.46	0.46	1.88	1.81	18.63	0.16	0.10	0.64	29.75	0.44	1.62	7.47	0.24	0.19	0.80	0.67	0.58	1.75	2.42	
Patenaude (2009) ³	[218]	Canada	37	1.00	22.57	6.84				0.51	2.05	22.24		0.75	30.17	0.18	1.47	7.44			0.78	0.73	1.62	2.34			
Philibert (2006) ³	[223]	Canada	243								24.19										0.57	1.33	1.90				
Austria (2008) ²	[28]	Canada	25																11	16	23	39					
Parkinson (1994)	[217]	USA-AY	20		16.61	7.51				2.54	18.22	30.57	0.16	0.55	5.27		0.41	6.41			5.22	11.63					
Parkinson (1994)	[217]	USA-AY	20		16.38	7.56				2.00	17.88	36.25	0.20	0.72	4.12		0.51	3.03			3.98	7.01					
Bagdade (1992)	[29]	USA	12																		1.25	1.94	3.19				
CDC (2012) ³	[226]	USA	1808	1.28	32.83	9.30	0.35	1.11	0.94	2.61	1.95	28.02	0.20	0.06	1.30	0.99	0.62	0.31	2.19	11.16	0.39	0.31	0.83	0.61	0.65	1.94	2.55
Conklin (2007) ³	[51]	USA	105									30.12			7.91		0.60	0.56			1.44	2.00					
Gong (1992)	[88]	USA	91		21.48	9.93					17.24	28.15	0.32	1.41	6.35		1.27	0.49	0.36	1.34	1.83						
Harris (2004)	[98]	USA	106									30.60	0.50	0.20	1.60	8.00	0.30	0.20	0.60	0.50	1.50	2.10					
Hibbeln (1998) ³	[106]	USA	49									32.30			7.26		0.21	0.56	0.56		1.62	2.19					
Hoffman (1993)	[113]	USA	20									28.86	0.43	0.41	2.28	8.98	0.50	0.28	0.44	0.56	0.63	1.99	2.55				
Ito (1999) ³	[120]	USA	124		24.96	8.17					22.46	0.81	30.85		1.60	7.56		0.75	0.97		1.88	2.85					
Keenan (2012) ⁴	[131]	USA	30	0.58	20.62	9.78			1.12		16.52	0.27	30.76	0.44	0.44	2.69	11.13	0.55	0.42	0.68	0.59	0.88	2.52	3.12			
Kelley (2008)	[132]	USA	24	1.30	22.30	6.20				1.52	21.85	26.94		1.50	5.90	0.25	0.32	0.77	0.92	0.69	1.18	2.10					
Lewis (2011)	[162]	USA	800	0.41	18.29	7.01	0.33	1.05	0.87	1.51	2.41	22.53	0.71	1.15	31.39	0.41	0.26	1.68	7.29	0.32	0.24	0.55	0.45	0.48	1.19	1.64	
Meydani (1991)	[192]	USA	23																		0.67	1.77	2.44				
Motoyama (2009)	[194]	USA	261									30.10			8.90		0.80	0.70	2.40	3.20							
Motoyama (2009)	[194]	USA	212									30.70			8.90		1.10	0.70	3.30	4.40							
Parkinson (1994)	[217]	USA	13		20.80	6.42			2.25		21.25	32.92	0.36	1.34	5.97		0.57	0.46			1.49	1.95					
Sekikawa (2008)	[251]	USA	281									30.80			8.90		0.40	1.00			3.20	4.20					
Sekikawa (2008)	[251]	USA	306									29.90			9.00		0.30	0.80			2.40	3.20					
Sun (2007)	[268]	USA	132	0.58	19.31	7.29			1.94		18.60	30.58			7.80		0.50	0.49	0.44		1.56	2.05					
Surette (2004) ³	[271]	USA	11	1.38	27.39	10.08				1.96	24.23	0.14	25.68	0.41	1.51	4.57	0.24	0.79	0.30	0.32	1.00	1.30					
Zhao (2012) ³	[303]	USA	23		25.59	12.06				1.53	17.70	32.13	0.52		7.47		0.72	0.50			1.78	2.28					
Johnson (2008) ²	[125]	USA	49																		20						
Sublette (2011) ²	[266]	USA	27																22	21	62	84					
Bloomer (2009) ²	[35]	USA	14																8	8	27	35					
Harper (2006) ²	[97]	USA	49							25		401			192		5	7	6	26	34						
High (2003) ²	[107]	USA	16									427	12		28	164		9			37	46					
Maki (2009) ²	[177]	USA	76																51		111	161					
Sublette (2007) ²	[265]	USA	10																25		68	94					
Central and South America																											
Brignardello (2011)	[38]	Chile	12	1.31	22.20	8.82				2.01	20.40	30.40		1.59	6.20		0.57	0.88			2.30	3.18					

¹Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion

²Data is ug/ml

³Weight % data calculated from concentration data in original manuscript

⁴Weight % data calculated from mole % data in original manuscript

CAN-CI, Canada -Cree/Inuit; NLD, The Netherlands; PNG, Papua New Guinea; Russia-IN, Russia Indigenous; S. Arabia, Saudi Arabia; SHB-SA, St. Helena Bay South Africa; S. Africa, South Africa; S. Korea, South Korea; UK, United Kingdom; USA, United States of America; USA-AY, United States of America -Alaskan Yupik.

"Western pattern" diets (Northern Russia, Alaska, Greenland, Papua New Guinea, Fiji, Nigeria, and the St. Helena Bay region of South Africa). Moderate blood levels of EPA + DHA (yellow) were observed in Northern Canada (Cree/Inuit populations), Chile, Iceland, Finland, Sweden, Tunisia, Hong Kong, Mongolia and French Polynesia. Europe had eight countries with low EPA + DHA blood levels (Belgium, Czech Republic, France, Germany, Scotland, Spain, and The Netherlands) while countries from the middle East (Israel), Asia (China, Russia, and Singapore), Oceania (Australia and New Zealand) and Africa (South Africa and Tanzania) were observed to have low levels as well. Very low blood levels were observed in North America (Canada and USA), Central and South America (Guatemala and Brazil), Europe (Ireland, UK, Italy, Greece, Serbia, and Turkey), the Middle East (Iran and Bahrain), Southeast Asia (India) and Africa (Kenya). The map also clearly indicates there are several regions with little to no blood fatty acid data for adult populations meeting our inclusion criteria (shaded in gray). This included most of Africa and the Middle East, Mexico and Central America, a considerable amount of South America, and most of Eastern Europe and Central and Southeast Asia.

4.3. Global distribution of individual n-3 LCPUFA

The levels of the individual n-3 LCPUFA were also examined against the EPA + DHA categories in the various blood fractions (Table 6). Each data line was assigned a blood level group based on the methodology used to determine groupings for the global map. Blood fractions were kept separate in order to examine and compare the responses of the individual n-3 LCPUFA within blood fractions. The mean values of the percentages of EPA, DHA and docosapentaenoic acid n-3 (DPAn-3, 22:5n-3) within a blood level category for each blood fraction were calculated.

DPAn-3 values were not reported as frequently as EPA or DHA (see details in Table 6 footnotes). In order to assist in comparing the response of EPA and DHA, the ratio of DHA to EPA, and the percentage of DHA in EPA + DHA was calculated. In general, DHA was the dominant contributor to EPA + DHA, but the relative amount of EPA tended to increase more as EPA + DHA status reached the highest category. The amount of DHA relative to EPA also tended to be higher in the blood fractions that were dominated by glycerophospholipids (plasma phospholipids and erythrocytes), while blood fractions with triacylglycerols and cholesterol ester components (plasma total lipids and whole blood) had slightly lower percentages of DHA. These latter blood fractions, tended to show shifts towards an increasing relative amount of EPA as EPA + DHA status increased as one ascended the categories, while the relative amount of EPA did not increase in glycerophospholipid based blood fractions until the high EPA + DHA blood level (green) was reached. While DPAn-3 also appeared to increase with EPA + DHA status, the increases tended to be relatively small in scale and absolute amount.

5. Discussion

This is the first systematic review to examine blood levels of omega-3 LCPUFA (specifically EPA + DHA) for different countries/distinct regions on a global scale. While the present review reveals considerable variability in blood levels of EPA + DHA, it also suggests that EPA + DHA blood levels are in the very low to low range for most of the globe especially when the population size of the countries [315] with very low and low blood levels of EPA + DHA are considered. There were several limitations and challenges in generating a global map of blood levels of EPA + DHA. This included numerous countries without data, data that

was limited to small sample sizes or data that was excluded because it did not meet criteria, but also the challenge of considerable variability in how fatty acid “levels” are reported. In addition, implications of the

present findings in terms of dietary intake and health outcomes as well as the challenge of increasing EPA + DHA blood levels must be considered. These topics will be taken up in the following sections.

Table 3
Global fatty acid compositions of plasma phospholipids expressed as relative percentages.¹

Author (Year)	Ref	Country	n	14:0	16:0	18:0	20:0	22:0	24:0	16:1 n-7	18:1 n-7	18:1 n-9	20:1 n-9	22:1 n-9	24:1 n-9	18:2 n-6	18:3 n-6	20:2 n-6	20:3 n-6	20:4 n-6	22:4 n-6	22:5 n-6	18:3 n-3	20:5 n-3	22:5 n-3	22:6 n-3	EPA+DHA	
Asia																												
Huang (2012)	[116]	China	940													23.58				11.05			0.32	1.36	1.08	5.49	6.85	
Zheng (2012)	[304]	China	100	0.36	28.26	14.51	0.37			0.49	1.25	8.69	0.93	0.45	0.73	21.01	0.61	0.39	2.10	9.15	0.22	0.23	0.15	1.48	0.79	5.79	7.27	
Hamazaki-Fujita (2011)	[96]	Japan	54		29.00	16.10						8.30			20.40					8.60			0.17	1.60		5.80	7.40	
Hojo (1998)	[114]	Japan	60		27.30	14.50						10.80			14.70					7.30				4.50		10.00	14.50	
Kawabata (2011)	[130]	Japan	104												19.70				1.70	7.60			0.20	2.30	0.90	5.60	7.90	
Kobayashi (2001)	[139]	Japan	87		28.70	15.10						8.80			17.30					6.40			0.20	3.70	1.20	7.30	11.00	
Kurotani (2012)	[148]	Japan	437		28.40	15.80				0.70		10.00			21.40					9.90			2.30	1.07	7.50	9.80		
Kusumoto (2007)	[149]	Japan	24		27.80	13.70						8.05			2.03	17.70				9.52				3.07	1.35	8.63	11.70	
Moriguchi (2004)	[193]	Japan	234																					2.86		3.08	5.94	
Watanabe (2009)	[292]	Japan	17		24.50	12.30						9.60				18.80				9.40				3.60		8.60	12.20	
Gerasimova (1991)	[86]	Russia	34		26.70	13.50				1.10		12.40				21.70				10.90				1.90	1.40	5.20	7.10	
Gerasimova (1991)	[86]	Russia-IN	11		28.50	11.20				4.40		16.80				12.30				4.60				5.40	1.50	5.50	10.90	
Kim (2012)	[136]	S. Korea	215		27.30	14.80	1.05			0.78		7.80				13.90	0.25	1.36	2.72	6.60			0.57	2.90		8.80	11.70	
Oceania																												
Hodge (1993) ²	[112]	Australia	7		28.83	11.97				1.27		13.33				26.84			3.45	9.34	0.27		0.36	0.63	0.73	2.99	3.63	
Hodge (2007)	[111]	Australia	4439		25.30					0.43		9.70				20.20				10.40			0.17	1.10		4.10	5.20	
James (2003)	[124]	Australia	44																				1.16	1.39	3.60	4.76		
Mantzioris (2000)	[179]	Australia	15												21.00				9.54			0.19	0.98	1.14	3.16	4.14		
McNaughton (2007) ²	[185]	Australia	43		26.53	14.71						9.83			20.94				10.59			0.12	0.84	1.11	3.70	4.54		
Metcalfe (2003)	[189]	Australia	16									9.80			20.90							0.23	1.13	1.39	3.76	4.89		
Stough (2012)	[264]	Australia	39																							3.45		
Dewailly (2008)	[68]	PFY	116																							5.01	6.11	
Crowe (2007) ³	[56]	N. Zealand	2416	0.52	35.38	17.82			2.08						23.14			3.51	9.48	0.68	0.69	0.30	1.36	1.29	3.76	5.12		
Middle East																												
Khanaki (2012)	[134]	Iran	74	0.26	48.53	13.35				0.39		6.28				19.66				7.23			0.35	0.36		0.70	1.06	
Europe																												
Crispim (2011)	[55]	Belgium	123																								5.30	
Maes (1999)	[174]	Belgium	14													22.11	0.21	0.30	2.24	9.25	0.46	0.24	0.22	1.08	0.94	3.81	4.89	
Rodriguez (2004)	[240]	Belgium	26	0.36	28.38	12.40	0.62	1.19	0.50	1.66	8.71			2.28	20.20		0.33		9.20		0.26	0.22	1.08	0.75	3.61	4.68		
Crispim (2011)	[55]	CZE	118																								4.20	
Hlavaty (2008) ³	[110]	CZE	39	0.34	27.53	13.04	0.03			0.74	1.60	12.31	0.14			21.89	0.08	0.48	3.21	11.64	0.30	0.20	0.22	1.08	0.85	4.32	5.40	
Astorg (2009)	[25]	France	222	0.51	27.11	12.74	0.22	0.35	0.30	0.78	1.79	9.94	0.18		0.45	22.19	0.11	0.34	2.62	10.02	0.28	0.27	0.25	1.10	0.91	4.31	5.41	
Crispim (2011)	[55]	France	111																								5.50	
Delyfer (2012)	[66]	France	107												18.70	3.00	0.30		12.00				0.20	1.20	0.90	4.50	5.70	
Saadatian-Elahi (2009)	[244]	France	96	0.26	24.80	14.30	0.03			0.76	1.50	9.40	0.19		22.30	0.08	0.36	3.30	12.50	0.37	0.25	0.16	1.40	1.14	6.30	7.70		
Geppert (2005)	[85]	Germany	108		28.10	12.00				0.60		10.30			22.30	0.11		3.40	8.90	0.41	0.35	0.21	0.57	0.87	2.70	3.27		
Geppert (2008)	[84]	Germany	39												0.10			3.27	9.38							3.21		
Saadatian-Elahi (2009)	[244]	Germany	386	0.28	25.90	12.00	0.02			0.70	1.50	10.20	0.21		22.70	0.10	0.36	3.40	11.80	0.37	0.26	0.21	1.20	1.12	4.60	5.80		
Saadatian-Elahi (2009)	[244]	Greece	191	0.21	24.50	14.30	0.04			0.45	1.55	11.75			23.20	0.09	0.33	3.70	11.00	0.33	0.24	0.13	1.05		5.45	6.50		
Saadatian-Elahi (2009)	[244]	Italy	578	0.24	25.20	14.10	0.03			0.50	1.60	11.90	0.17		21.00	0.10	0.34	4.00	12.40	0.41	0.34	0.14	0.90	0.93	4.60	5.50		
Di Stasi (2004) ⁴	[70]	Italy	36																				0.65		3.30	3.95		
Masson (2013) ⁴	[181]	Italy	1203																			0.11	0.85	0.78	3.37	4.22		
Leng (1994)	[160]	Scotland	122		28.00	10.30						13.06			25.86	0.01		2.81	9.14	0.18	0.17	0.31	1.45	0.91	3.89	5.34		
Leng (1999)	[161]	Scotland	770									12.63			24.37			2.96	9.27			0.31	1.42		3.81	5.23		
Surai (2000)	[270]	Scotland	40		26.80	13.90						12.00			22.20			3.50	9.50				1.50	1.20	3.90	5.40		
Saadatian-Elahi (2009)	[244]	Spain	193	0.19	23.80	15.10	0.03			0.40	1.60	11.90	0.16		21.90	0.09	0.36	3.60	11.90	0.34	0.24	0.11	1.10	0.77	6.00	7.10		
Saadatian-Elahi (2009)	[244]	Spain	196	0.18	23.90	15.10	0.03			0.40	1.60	10.90	0.15		22.30	0.09	0.36	3.40	11.80	0.31	0.21	0.13	1.50	0.85	6.40	7.90		
Saadatian-Elahi (2009)	[244]	Spain	194	0.19	24.20	14.70	0.03			0.50	1.50	10.80	0.16		23.00	0.09	0.35	3.30	12.00	0.33	0.22	0.11	1.30	0.80	6.10	7.40		
Saadatian-Elahi (2009)	[244]	Sweden	388	0.28	25.90	13.80	0.02			0.60	1.70	11.20	0.23		22.00	0.07	0.34	3.10	10.00	0.28	0.17	0.28	1.80	1.24	5.80	7.60		
Crispim (2011)	[55]	NLD	120																								4.60	
De Groot (2008)	[64]	NLD	46																					0.84		3.09	3.93	
deGroot (2007)	[62]	NLD	54																					0.75	0.75	3.22	3.97	
deGroot (2009)	[63]	NLD	234												21.83	0.08		3.18	9.61	0.29	0.23	0.18	0.99	0.92	3.45	4.43		
Saadatian-Elahi (2009)	[244]	NLD	195	0.28	25.35	14.20	0.03			0.60	1.50	9.40	0.21		24.40	0.09	0.36	3.50	11.50	0.37	0.25	0.21	1.20	1.15	4.40	5.60		
Sobczak (2004)	[257]	NLD	15												19.80		0.31	2.65	8.53	0.58	0.21	0.31	0.99	0.78	3.61	4.60		
Tiemeier (2003)	[276]	NLD	461												21.80			3.30	9.00									

Table 3(continued)

Africa																												
Glew (2010)	[87]	Nigeria	51	0.22	30.20	12.90	0.18		0.41	1.09	10.00		0.43	19.90	0.14	0.38	3.51	14.10	0.79	0.63	0.18	0.42	0.92	3.14	3.56			
Njelekela (2005)	[205]	Tanzania	36	0.70	28.20	14.90					13.80			13.60				5.80	0.70	1.10	0.70	1.10	1.40	2.50				
Njelekela (2005)	[205]	Tanzania	37	0.30	27.80	15.50					13.80			14.10				7.00	0.90	1.10	0.90	1.10	1.20	2.30				
Njelekela (2005)	[205]	Tanzania	32	0.50	27.20	15.30					15.50			15.10				4.80	1.00	0.80	1.00	0.80	0.50	1.30				
North America																												
Allard (1997)	[17]	Canada	72								11.25			25.31				13.64			1.11		3.99	5.10				
Conquer (1996)	[53]	Canada	24		26.60	13.00								22.40				3.00	9.30	0.28	0.25	0.26	0.60	0.92	2.30	2.90		
Conquer (1999)	[52]	Canada	19		28.20	14.20								18.90				2.70	10.80	0.77		0.17	0.99	1.02	2.90	3.89		
Conquer (2002)	[54]	Canada	10		26.30	14.20					9.30			20.80				4.10	11.80	0.33	0.01	0.20	0.95	0.92	3.30	4.25		
Cunnane (1995)	[57]	Canada	10																		0.40	0.80	1.10	3.60	4.40			
Dewailly (2001)	[69]	Canada	1460															6.40				0.52	1.28	1.79				
Garneau (2012)	[83]	Canada	198																		0.17	1.08	0.95	3.21	4.29			
Laurin (2003)	[153]	Canada	79																			0.58	2.13	2.71				
Liou (2007)	[165]	Canada	22		26.30	13.90												10.20				0.27	1.35	4.59	5.94			
Metherell (2012)	[191]	Canada	8	0.55	28.44	16.14	0.40	1.10	1.06	0.46	1.69	12.60	8.05	0.16	0.10	1.39	19.33	0.08	0.32	2.73	9.89	0.37	0.40	0.20	0.73	0.84	2.75	3.48
Skuladottir (1995)	[256]	Canada	119	0.55	32.22	15.36				0.91	14.13	18.89						2.16	6.73			0.76	0.55	1.39	2.15			
Stark (2000)	[262]	Canada	35		27.30	13.80					12.20	17.50						2.90	10.00			1.10	0.84	3.70	4.80			
Stark (2002)	[261]	Canada	16		25.49	13.19	0.59	1.89			12.55	18.40	0.58	0.14				2.57	10.03	0.99	0.33	0.17	1.30	1.03	4.23	5.53		
Stark (2004)	[260]	Canada	32		27.75	13.11	1.25	0.94	0.64		12.51	18.96			1.92			3.29	10.65	0.41	0.27	0.25	1.03	0.95	3.89	4.92		
Dewailly (2002)	[67]	CAN-CI	917															0.86				9.16	3.02	12.18				
Lucas (2009)	[171]	CAN-CI	698									18.50						9.30				0.21	0.93	0.74	3.10	4.03		
Lucas (2009)	[170]	CAN-CI	297									18.30						6.30				0.20	3.50	1.40	5.30	8.80		
Stark (2002)	[261]	Greenland	15		26.60	13.89	0.50	1.35			13.20	13.97	0.49	1.15	5.24	0.49	0.05	5.24	0.49	0.05	0.14	4.90	1.62	7.89	12.79			
Antalis (2006)	[23]	USA	12	1.36	26.57	13.71	0.01	0.22	0.16	0.47	2.06	8.75	0.02			0.20	25.95	0.36	2.98	11.40	0.44	0.27	0.10	0.68	0.90	2.96	3.64	
Arterburn (2007)	[24]	USA	12									21.65	0.11	0.38	3.36	13.40	0.60	0.33	0.22	0.72	0.94	0.22	0.72	0.94	3.22	3.94		
Brasky (2011)	[37]	USA	1803									19.56						11.18				0.14	0.57	2.84	3.41			
Cao (2006)	[42]	USA	19																						4.23			
Cunnane (2012) ²	[58]	USA	10		27.14	16.43			0.57		9.79	16.50						11.43				0.07	0.64	0.79	3.36	4.00		
de Oliveira Otto (2013)	[65]	USA	2837									21.40						12.00				0.18	1.00	1.00	4.20	5.20		
Harris (2007)	[100]	USA	23															12.60				0.55			3.03	3.58		
Lopez (2011)	[168]	USA	267																						1.54			
Mozaffarian (2011)	[196]	USA	2735																			0.59	0.83	3.03	3.62			
Mozaffarian (2013)	[195]	USA	2692																			0.51	0.82	2.87	3.38			
Muldoon (2010)	[197]	USA	280																			0.16	0.49	1.52	2.01			
Phinney (1990)	[224]	USA	100			12.53	0.33	1.11			8.87	23.90			0.47	3.41	12.81					0.21	0.59	3.59	4.18			
Raatz (2009)	[227]	USA	10	0.37	26.38	12.32					8.87	25.47	0.14					11.06				0.28	0.53	0.77	2.37	2.90		
Wang (2003)	[291]	USA	3309		25.40	13.30				0.64	8.60	22.00	0.11					3.32	11.50			0.15	0.56	2.80	3.36			
Young (2011)	[300]	USA	17									21.53						9.25				0.29	0.81	2.22	3.03			
<i>Liu (2011)⁴</i>	[166]	USA	265																			0.50		1.53	2.03			
<i>Raatz (2013)⁴</i>	[228]	USA	19															17.12	0.76			0.87	1.55	3.22	4.09			
<i>Young (2013)⁵</i>	[301]	USA	17															286				4	11	10	30	41		
Central and South America																												
Fillion (2011)	[80]	Brazil	243																			0.44	1.98	2.42				
Moriguchi (2004)	[193]	Brazil	160																			1.47	1.06	2.53				

¹Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion

²Weight % data calculated from concentration data in original manuscript

³Weight % data calculated from mole % data in original manuscript

⁴Data is mole %

⁵Data is µg/ml

CAN-CI, Canada –Cree/Inuit; CZE, Czech Republic; NLD, The Netherlands; N. Zealand, New Zealand; PYF, French Polynesia; Russia-IN, Russia Indigenous; S. Korea, South Korea; UK, United Kingdom; USA, United States of America.

5.1. Countries with limited, excluded or no data

Data was not found for most of Africa, Eastern Europe, the Middle East and Central Asia, Southeast Asia, and Central and South America. Based on the data in neighboring countries, it is most likely that blood levels of EPA + DHA in Eastern Europe and Central Asia would fall in the low to very low categories. Similarly, most of the countries in Central and South America would most likely fall into the lower blood level categories, although some of the countries with large coastal populations could fall into the higher categories. Africa might follow a similar pattern as South America but the limited blood fatty acid data and the small samples sizes reported for this continent make it difficult to predict. For countries of Southeast Asia for which we found no data, it is possible that many of them would have blood EPA + DHA levels in the higher categories. While these speculations are based on blood level patterns in and surrounding these geographical regions, recently published data on omega-3 PUFA intakes across the globe (see detailed discussion below in Section 5.3) appear to support these assumptions [4].

In addition to countries without blood level data, there are several countries with blood levels that are based on limited numbers of studies and small sample sizes. While this can be expected for small or developing countries, it is a concern when large countries, with large populations such as Russia and India have limited data. For some of the countries with limited or no data in this review, fatty acid compositional data of human blood exists, but not for the general adult population. While some data was excluded due to the study of blood fatty acids in morbidity or disease, several studies were excluded because the participants were pregnant women or children. For example, data on erythrocyte levels of pregnant women in Mexico is available [316], but we were unable to find data for the general adult population in Mexico. Also with any systematic review, new studies meeting inclusion criteria may be published after analysis is complete. However, new studies may not

change the global map assignments. For example, the EPA + DHA levels recently presented in a large study (n = 826) examining the plasma fatty acids of healthy students at the University of Toronto (Canada) [317] confirm the global map assignment for Canada based on prior data.

Finally, there was evidence of significant regional and cultural variation in blood levels of EPA + DHA within certain countries. In particular, populations living on coastal regions of countries, and populations that traditionally rely on hunting, fishing and gathering for sustenance tended to have moderate to high blood levels of EPA + DHA. This latter observation tends to be supported by assessments of changes in the consumption of omega-3 PUFA in North America with the expansion of and dependency on industrial scale agricultural practices [318]. It was also interesting that there was a tendency of these populations to be oversampled relative to the rest of the country, particularly in Russia, but also in Canada. This could reflect a bias against funding towards the collection of “normative” data that should be reconsidered, as standard ranges are necessary as a reference for proper comparisons and establishing normal values.

5.2. Units for expressing fatty acid compositional data

The lack of a “gold standard” for measurement of fatty acid status in human blood makes it very difficult to compare studies across the globe. The lack of a standardized method for measurement was first highlighted in 2004 by Harris and von Schacky when the omega-3 index was first proposed [313]. At the time, erythrocytes were identified as the potential standard of the future, but a widespread shift to erythrocyte fatty acid analysis has not occurred. This is partly based on logistical challenges with erythrocyte sample preparation and storage [319–321]. The diversity in the choice of units for reporting fatty acid data also remains a challenge. Based on studies included in this systematic review,

Table 4(continued)

Africa																														
Knoll (2011)	[138]	Kenya	18	0.42	28.22	11.78						0.50	17.06	12.93	0.07	13.66	0.16	0.84	2.84	2.23	3.07									
North America																														
Edwards (1998)	[74]	Canada	14																0.12	0.73	2.03	4.72	5.45							
Kröger (2009)	[142]	Canada	514																0.64	2.38	3.58	4.22								
Lucas (2009)	[169]	Canada	65													9.99			0.18	0.86	2.33	3.73	4.50							
Metherell (2009)	[190]	Canada	16	0.69	22.89	13.21	0.26	1.04	2.80	0.36	1.47	12.76	0.27	2.74	9.83	0.01	1.48	12.16	3.06	0.32	0.12	0.35	1.77	2.98	3.33					
Metherell (2012)	[191]	Canada	8	1.40	21.84	12.48	0.32	1.37	4.31	0.25	1.31	11.82	0.24	0.08	3.74	10.18	0.04	0.26	1.46	13.70	3.34	0.57	0.16	0.65	2.39	4.03	4.68			
Nagasaka (2014) ^{2,7}	[200]	Canada	649	0.39	26.00	21.51	0.26	0.43	1.09						13.75			2.07	19.30	3.51	0.56	0.24	1.29	3.35	6.25	6.23				
Barcelo-Coblijn (2008) ³	[31]	Canada	62												13.68				18.01	2.60		0.36	0.74	2.18	3.09	3.83				
Lucas (2010)	[172]	CAN-CI	649												10.50			1.77	11.50		0.44	0.03	1.67	2.17	5.39	7.06				
Valera (2011)	[283]	CAN-CI	181																			2.10	6.70	8.80						
Zhou (2011)	[305]	CAN-CI	2200																			1.10	1.40	2.60	3.70					
Thorseng (2009)	[275]	Greenland	452																		0.18	2.70	2.10	6.40	9.10					
Ebbesson (2010)	[73]	USA-AY	707			20.90																2.20	6.70	8.90						
Makhoul (2011)	[176]	USA-AY	330																			2.80	6.80	9.60						
O'Brien (2009)	[209]	USA-AY	496																			2.40	6.40	8.80						
Antalis (2006)	[23]	USA	12	0.27	21.11	15.10			0.34	0.30	2.06	14.32	0.19		0.20	12.90		0.30	1.60	15.75	4.31	0.71	0.56	2.71	4.65	5.21				
Arterburn (2007)	[24]	USA	12													13.70	0.08	0.32	1.73	14.29	3.94	0.51	0.18	0.57	2.00	3.53	4.10			
Aupperle (2008)	[27]	USA	33	0.23	20.01	16.19	0.20	0.23	1.68	0.21				11.96	1.20	1.62	11.40	0.04	0.24	1.05	17.15	4.14	0.76	0.09	0.41	2.13	3.76	4.17		
Block (2008)	[34]	USA	768																			0.72		3.53	4.25					
Cao (2006)	[42]	USA	9																			0.60	1.80	3.80	4.40					
Harris (2007)	[100]	USA	23																			0.90	3.28	4.18						
Harris (2008)	[99]	USA	33																			0.47	3.67	4.14						
Harris (2012)	[101]	USA	291	0.34	21.50	17.70			0.44	0.38				13.80	0.23		0.43	11.00	0.06	0.29	1.65	16.80	3.83	0.70	0.20	0.60	2.59	4.76	5.36	
Hoffman (1993)	[113]	USA	20													12.60	0.04	0.41	1.99	16.24	4.73	0.87	0.11	0.43	2.27	3.91	4.34			
Keenan (2012) ²	[131]	USA	30	0.24	19.25	18.31			0.21					13.13	0.30			13.04	0.10	0.35	1.97	19.60	4.99	1.02	0.14	0.41	2.72	4.23	4.63	
Kelley (2008)	[132]	USA	20	0.33	26.64	11.91								17.09				13.53			1.82	13.56	3.61	0.48	0.18	0.47	1.77	2.69	3.16	
Ladesich (2011)	[151]	USA	228	0.35	21.00	18.00			0.38	0.32				14.00	0.16			0.38	12.00	0.11	0.24	1.60	17.00	4.00	0.74	0.20	0.53	2.60	4.10	4.63
Lemke (2010)	[159]	USA	252																			16.95		0.45	2.55	3.85	4.31			
McNamara (2010)	[184]	USA	20		16.90	16.40								1.20	11.90			10.90		1.50	16.90	4.00	0.80	0.40	2.30	4.40	4.80			
Newcomer (2001)	[203]	USA	156																			14.04		0.19	0.61	4.17	4.78			
Sun (2007)	[268]	USA	132	0.19	18.65	13.14			0.49													13.66	14.63	0.18	1.15	1.85	3.71	4.86		
Reddy (2004) ⁸	[231]	USA	31													317						339	60	40	69	61				
Central and South America																														
Elizondo (2007)	[75]	Chile	8	0.88	16.80	19.50	1.24	1.32						2.27		7.81						0.85	17.20		1.75	0.58	2.61	7.12	15.20	17.81
Solomons (2015)	[259]	Guatemala	158	0.71	27.09	9.66			0.36	0.87	1.57	15.80	0.22			0.30	16.37	0.11				2.58	12.88	3.79	0.84	0.27	0.35	1.78	3.09	3.43

¹Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion
²Weight % data calculated from mole % data in original manuscript
³Data is mole %
⁴Data is µg/mL
⁵Weight % data calculated from concentration data in original manuscript
⁶Data is µg/mg
⁷EPA+DHA was presented as weight % in original manuscript
⁸Data is nmol/mL
 CAN-CI, Canada-Cree/Inuit; NLD, The Netherlands; N. Zealand, New Zealand; Russia-IN, Russia Indigenous; Russia-PK, Russia Primorsky Krai; S. Korea, South Korea; UK, United Kingdom; USA, United States of America; USA-AY, United States of America-Alaskan Yupik.

the apparent preferred manner for presenting fatty acid data is as relative weight % of the total fatty acids. The advantage of relative percentage data is that it simplifies the comparisons of the complex interactions between fatty acids competing for positions in the blood lipidome and allows for an assessment of the “quality” of the fat. However, as a “relative” unit, percentage fatty acid data should be presented as full fatty acid profiles to allow proper interpretation of the changes in the profile. A limitation of relative percentage data is that it can obscure and potentially mask changes in the size of lipid pools. In the blood of normal, healthy adults, the changes in lipid pools in blood should be minimal in erythrocytes and plasma phospholipids. However, the plasma total lipid pool is subject to considerable biological variation even in healthy populations based largely on lipoprotein status, particularly in the triacylglycerol content even when fasting and feeding is controlled [191,314,322]. The use of relative percentage units also presents a challenge for performance elements and validation methods for standardized clinical testing as limits of detection and repeatability are measures based on absolute concentrations of individual analytes [323]. While the omega-3 index increased awareness and the clinical use of omega-3 biomarkers [324], it has likely contributed to the practice of not presenting relative percentage data as full fatty acid profiles particularly in large intervention trials focused on clinical outcomes [325,326]. The omega-3 index was initially described as the sum of the relative weight percentage of EPA + DHA with respect to the total fatty acids in erythrocytes [313], but total fatty acids is a vague term and the sum total of fatty acids can differ depending on the expertise of the chromatographer and the little discussed practice of reporting data as total fatty acids “identified” vs. total fatty acids that include peaks that were not identified (the sum of the total peak area). Also, total fatty acids available for analyses can also be influenced by sample preparation techniques, particularly extraction and derivitization protocols [311], but also analytical practices with gas chromatography and data handling such as the application of response factors [327]. The increasing use of whole blood as dried blood spots has further complicated the ability to standardize “the omega-3 index” as whole blood measures are mathematically

translated based on calculations based on the relationship to the omega-3 index in erythrocytes [328]. Unfortunately, detailed methodologies employed are not consistently reported in the literature. Therefore a standardized measure of omega-3 status across laboratories capable of fatty acid determinations does not currently exist and authors must be encouraged to provide more details on how relative percentage data were calculated. In addition, authors should be encouraged to include an internal standard in their analyses so as to allow the report of the concentration of total fatty acids in addition to the weight % data as it allows for the conversion of fatty acid data between different units of measure and therefore enables literature comparisons. In this review, studies using the fatty acid composition of plasma total lipid, plasma phospholipid, erythrocytes and whole blood were included. Fatty acid data from serum fractions were considered equivalent to data from plasma fractions, and data from erythrocyte phospholipids and erythrocyte membrane preparations were considered equivalent to data from erythrocytes. There are several other blood fractions that have been examined in the literature, but they were not included in the present review due to limited prevalence and an increased challenge to translate the data to erythrocyte EPA + DHA equivalents. These include mononuclear cells and platelets but also phosphatidylcholine, cholesteryl ester, nonesterified fatty acid, and triacylglycerol fractions in plasma [321,329]. The relationship between EPA + DHA levels in cholesteryl ester, nonesterified fatty acid, and triacylglycerol fractions in plasma and levels in erythrocytes has been shown to be weaker than those between the pools examined presently [314]. Although, the number of studies reporting whole blood EPA + DHA data were much smaller, whole blood data was included as this type of analysis is increasing and will likely become a very common method in the future as dried blood spot blood collections enable economical high throughput fatty acid profiling [311]. The ease of collection and processing for dried blood spot sampling has great potential for field studies [191,311,330,331] particularly in developing countries where scientific resources are limited [332]. Dried blood spotting also has the potential to solve challenges around the storage of blood samples [191,319,320].

Table 5
Global fatty acid compositions of whole blood total lipids expressed as relative percentages.

Author (Year)	Ref	Country	n	14:0	16:0	18:0	20:0	22:0	24:0	16:1 n-7	18:1 n-7	18:1 n-9	20:1 n-9	22:1 n-9	24:1 n-9	18:2 n-6	18:3 n-6	20:2 n-6	20:3 n-6	20:4 n-6	22:4 n-6	22:5 n-6	18:3 n-3	20:3 n-3	22:5 n-3	22:6 n-3	EPA+DHA	
Europe																												
Rizzo (2010)	[238]	Italy	300		22.63	11.28				1.50	23.97					21.61		1.95	11.19				0.45	1.05	1.26	3.11	4.16	
Rizzo (2012)	[237]	Italy	76																					1.04	2.89	3.93		
Scandinavia																												
Jabbar (2006)	[123]	Sweden	18	1.12	25.65	11.11	0.38		2.79	1.96	1.88	19.84				21.09		1.35	6.93	0.55		0.70	1.19		2.62	3.81		
North America																												
Fratesi (2009)	[6]	Canada	15	2.50	28.70	11.40	0.40	0.70	1.00	2.20	1.80	15.10			1.00	16.20	0.40	0.70	1.10	6.40	0.60		0.50	0.80	0.70	1.90	2.70	
Metherel (2009)	[190]	Canada	16	0.85	22.45	9.68	0.17	0.47	0.90	1.71	1.86	18.12	0.28		1.00	21.90	0.19		1.50	8.79	1.29	0.32	0.41	0.34	0.93	1.87	2.21	
Metherel (2012)	[191]	Canada	8	0.98	22.63	12.29	0.34	0.88	1.40	1.31	1.62	16.18	0.19	0.29	1.42	22.05	0.33	0.24	1.48	9.35	1.10	0.29	0.60	0.61	1.00	2.04	2.65	
Patterson (2012)	[5]	Canada	78																							1.95	2.56	
Albert (2002)	[14]	USA	184		18.80	10.60						17.00				24.20				10.60			0.37	1.84	1.01	2.38	4.22	
Hall (2007)	[94]	USA	282												24.36					9.93			0.36	1.87	0.96	2.27	4.14	
Harris (2007)	[102]	USA	94																					0.57	1.84	2.41		
Pottala (2010)	[225]	USA	956																							3.80		
Ramsden (2010)	[229]	USA	15													23.20	0.20	1.59	7.17	0.33		0.46	0.46	0.97	2.71	3.17		

USA, United States of America.

5.3. Diet and blood

Blood levels of EPA + DHA have long been known to correspond to dietary intakes of EPA + DHA [139,190,333,334]. Recent studies examining the determinants of blood levels of EPA and DHA consistently indicate that diet is the main predictor although other factors such as age, smoking, sex, and physical activity are commonly identified as predictors as well [8–12]. In addition, genotyping studies have linked single nucleotide polymorphisms of FADS1, FADS2, FADS3 and ELOVL2 [335–337] to slightly increased levels of EPA + DHA. Recently a unique FADS haplotype more efficient at biosynthesizing DHA has been identified in humans as compared with hominid ancestors [335], and supports the hypothesis that DHA was important for the evolution of the human brain [338]. The complex relationship between dietary fatty acid intake and blood levels of long chain PUFA including EPA and DHA were first empirically defined by Lands et al. in rats [339], adapted to humans [340] and then further revised as data from other

populations became available [341]. Despite these robust equations, this previously defined relationship between dietary intake and blood levels is often forgotten when examining increases in EPA + DHA in blood relative to prescribed dose in dietary intervention studies [342]. Recently, the simple relationship between dietary EPA + DHA and blood levels of EPA + DHA have been examined and it appears that simple linear equations can be used to define the blood-diet EPA + DHA for intakes typical of Western populations and possibly higher intakes [343].

Global intakes of dietary fats and oils derived from nutrition surveys have been examined at the national level for adults recently that included a map of seafood omega-3 fat intake [4]. As suspected, the seafood omega-3 map shares several similarities with the map of blood levels presented herein (Fig. 2), but there are also distinctive differences. The seafood omega-3 fat intake is more comprehensive as intake data was available for Africa, Eastern Europe, the Middle East and Central Asia, Southeast Asia, and Central and South America, where we were unable

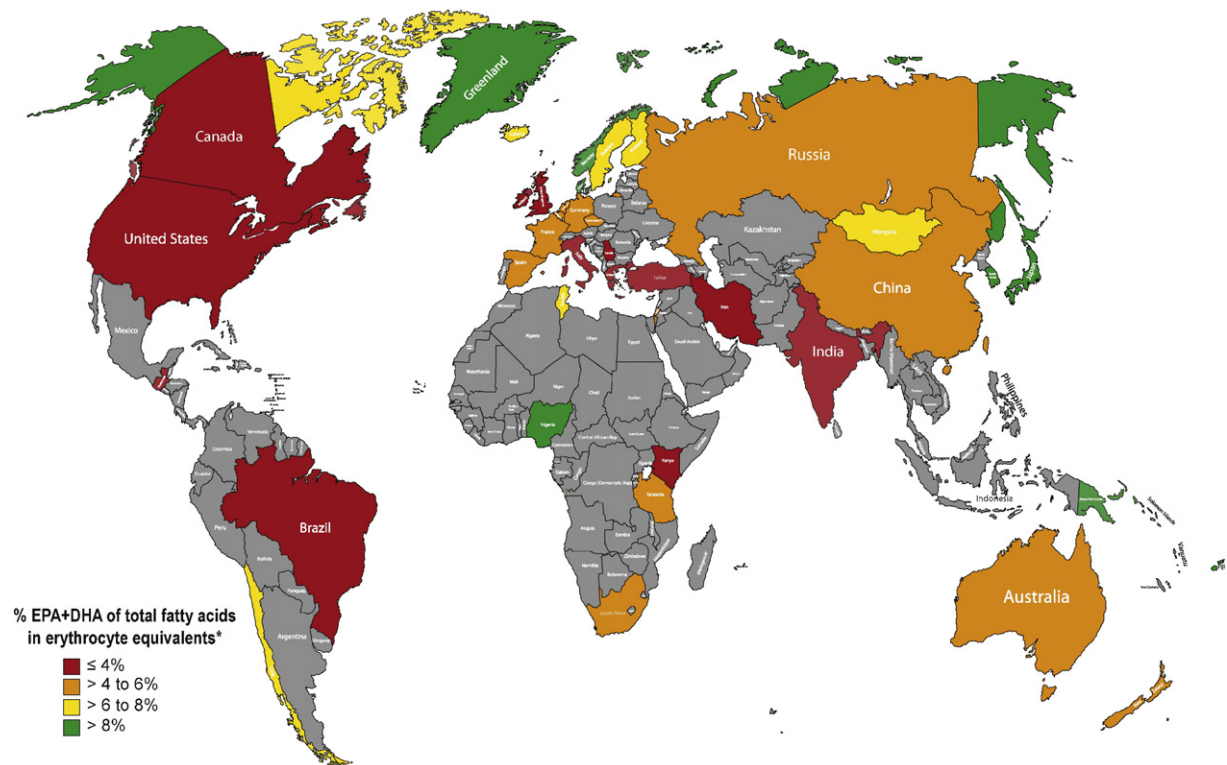


Fig. 2. Global blood levels of the sum of eicosapentaenoic acid and docosahexaenoic acid. *Fatty acid composition data from plasma total lipids, plasma phospholipids and whole blood were assigned to categorical ranges that were estimated as equivalent to erythrocyte categories [314].

Table 6

Percentages of individual long chain omega-3 by stratifications within blood fraction.

EPA + DHA categories	Map color	Number of studies	EPA	DPAn-3*	DHA	EPA + DHA	DHA:EPA ratio	DHA/EPA + DHA %
			weight % of total fatty acids					
Plasma total lipid								
≤2.9	Red	43	0.57	0.49	1.55	2.12	2.71	73.0
>2.9–4.0	Orange	24	1.02	0.58	2.35	3.37	2.31	69.7
>4.0–5.2	Yellow	14	1.30	0.67	3.11	4.41	2.40	70.6
>5.2	Green	25	2.91	0.98	5.27	8.18	1.81	64.5
Plasma phospholipid								
≤3.8	Red	25	0.66	0.86	2.18	2.85	3.29	76.7
>3.8–5.7	Orange	38	1.03	1.01	3.75	4.81	3.64	78.0
>5.7–7.6	Yellow	23	1.61	1.04	5.05	6.66	3.13	75.8
>7.6	Green	25	2.93	1.23	6.84	9.77	2.33	70.0
Erythrocytes								
≤4.0	Red	40	0.49	2.01	2.71	3.20	5.48	84.6
>4.0–6.0	Orange	41	0.68	2.18	4.14	4.82	6.07	85.9
>6.0–8.0	Yellow	19	1.04	2.40	5.86	6.83	5.62	85.7
>8.0	Green	20	2.48	2.92	7.84	10.33	3.16	75.9
Whole blood								
≤3.0	Red	5	0.59	0.88	1.92	2.51	3.28	76.6
>3.0–4.4	Orange	6	1.24	1.05	2.66	3.91	2.14	68.2
>4.4–5.9	Yellow	0	–	–	–	–	–	–
>5.9	Green	0	–	–	–	–	–	–

Fatty acid values are the average of values reported for each individual study. *Studies reporting DPAn-3 values for: Plasma total lipid were 24 red, 12 orange, 10 yellow and 17 green; Plasma phospholipid were 10 red, 32 orange, 14 yellow and 15 green; erythrocytes were 31 red, 35 orange, 14 yellow, and 13 green; whole blood were 3 red and 4 orange. EPA, eicosapentaenoic acid (20:5n-3); DPAn-3, docosapentaenoic acid n-3 (22:5n-3); DHA, docosapentaenoic acid (22:6n-3).

to find EPA + DHA blood data, although the one exception was the inclusion of blood data for Greenland where no dietary survey data was reported. While low to high blood categorizations tend to agree with low to high diet intake categorizations, there were some notable exceptions. A disconnect between dietary intake and blood levels could be the result of documented limitations of determining fatty acid intakes from databases [5], but it may also be due to challenges in blood fatty acid analysis. Countries with the highest seafood omega-3 intake consumption included the Pacific island nations, the Mediterranean basin, Iceland, South Korea and Japan. Blood EPA + DHA levels were also high in South Korea, Japan, and the few countries we had for Pacific island nations, but blood levels of EPA + DHA for the Mediterranean basin were low to very low while Iceland blood levels were moderate. Given dietary levels, moderate blood levels of EPA + DHA for Iceland were somewhat surprising and more data may be required to confirm this assessment. One of the four studies for Iceland that indicated moderate blood levels of EPA + DHA in erythrocytes stored the blood samples at -20°C for 15 weeks [175] which is known to promote EPA + DHA losses [319]. However, prior to storage, butylated hydroxytoluene was added to the samples that have the potential to protect samples from decreases in EPA + DHA [320,344]. In addition, one of the Icelandic studies was a direct comparison to populations from Japan and Korea and while the per capita consumption of fish and shellfish was the highest in Iceland, measured blood levels of EPA + DHA were high in the Japan and South Korea samples and moderate in the Iceland sample [252]. For the Mediterranean Basin, it is difficult to determine the cause of discrepancies between intakes of seafood omega-3 fat and blood levels. Blood level data was available from several studies for these countries. The low blood levels could indicate a bias in regard to the type of populations that were sampled. For example, blood sampling itself might lend itself to urban centers where the chance of shifts away from more traditional diets is increased. It may also reflect differences in how we categorized blood levels relative to how dietary intake levels were categorized and they do not necessarily match. Based on calculations from a recent study examining the relationship between dietary intakes and blood levels of EPA + DHA with a typical North American background diet [343], intakes of approximately 200 mg/day EPA + DHA would be required to shift blood EPA + DHA levels from the very low (red) to low (orange) blood levels and approximately 500 mg/day to shift to moderate (yellow) blood levels. Obtaining high blood levels of EPA + DHA (corresponding to >8% in erythrocytes) would appear to require at

least of 1250 mg/day EPA + DHA with a North American diet [343]. Background diet may influence this intake requirement as dietary EPA + DHA intake estimates from Japan can range from 669 to 1120 mg/day in adult populations [345] while studies in the present review reported EPA + DHA in erythrocytes ranging from 5.9 to 14.4%. The highest category in the global seafood omega-3 fat intake mapping study was >550 mg/day [4] which may not be high enough to discriminate the global EPA + DHA status given that there are recommendations of ≥ 1000 mg/day EPA + DHA from more than one expert group [346,347].

5.4. Potential consequences of low blood levels of EPA + DHA

Low blood and dietary intake of EPA + DHA can potentially increase the risk of adverse health outcomes. While EPA + DHA is often presented as a panacea, the strongest evidence for health benefits of increased EPA + DHA status have been found for reducing the risk of coronary heart disease and possibly total mortality, and for supporting fetal/infant neurodevelopment [348,349] and the latter is mechanistically related to cognitive function throughout the lifespan. While there are no Dietary Reference Intakes for EPA and DHA, it has been proposed [346, 348] and several expert groups and international bodies have established recommendations that typically range from 250 mg/day to 500 mg/day EPA + DHA for general health and 500 mg/day to ≥ 1000 mg/day EPA + DHA for heart health as reviewed and discussed previously [343,346,347]. These intake recommendations align closely with the intakes associated with the erythrocyte blood level categories that were used to develop the current global map, therefore we can conclude that global blood levels of EPA + DHA are also low as a result of intakes lower than expert group recommendations.

The initial observations focusing on different blood lipids in the Greenland Inuit [350,351] suggested cardiovascular benefits of a marine diet. The validity of the mortality records of the Greenland Inuit during these initial observations been questioned in the past [352] and more recently [353], but interpreting cardiovascular mortality prevalence in Greenland during this period is challenging due to high rates of violent death in males [354] and very high rates of smoking [355]. Autopsy studies, although limited, have suggested that atherosclerosis is reduced in Greenland and Alaskan natives as compared with non-natives [356, 357]. Nevertheless, these initial observations in Greenland led to intervention studies examining oily fish intake [358] and fish oil

supplementation [359] that established a link between EPA + DHA intake and reduced risk of coronary heart disease mortality with a major proposed mechanism of a reduction in fatal arrhythmias and sudden cardiac death. Various observational cohort studies that followed provided further support for the benefits of EPA + DHA by linking blood levels of EPA + DHA to cardiac events [13,14,360]. Numerous mechanisms appear to be responsible for the cardiovascular effects of EPA + DHA. These include altering biophysics properties of cellular membranes, modulating membrane proteins and ion transport, influencing gene expression directly and indirectly and serving as substrates for the production of potent metabolites or lipid mediators [361]. With these multiple mechanisms, omega-3 LCPUFA therefore have numerous physiological effects that have been confirmed by meta-analyses and include reduced resting heart rate [362], influencing heart rate variability [363], reduced blood pressure [364], reduced blood triglycerides [365,366] and reduced thrombosis [361]. It has been proposed that most of the benefit of EPA + DHA could be achieved with relatively modest intakes of EPA + DHA (250–500 mg/day) [349] which would be associated with modest increases in blood levels [343]. However, the reduction of secondary coronary events through EPA supplementation in a Japanese population with a high background diet of EPA + DHA [367] suggests higher dietary targets and blood levels should be considered. A recent examination of the dietary intakes of EPA + DHA and blood levels indicates that intakes of 250–500 mg/day EPA + DHA do not increase blood EPA + DHA to levels associated with reduced cardiac events in previous cohort studies [343]. Recently, the benefits of EPA + DHA intake for reducing coronary heart disease mortality have been questioned due to a lack of an effect in several recent trials [325,326,368–370]. The recent clinical trials have been criticized for being underpowered [371], low intervention doses [372], a lack of attention to baseline intake of EPA + DHA [373,374] and for overestimating adherence and compliance [7,373]. In addition, the relationship between EPA + DHA and arrhythmias has been shown to be inconsistent which is in part due to considerable heterogeneity in study populations and study design [375]. It has also been suggested that the anti-arrhythmic effect may only be beneficial in life threatening ischemia-induced ventricular fibrillation and not recurrent ventricular or atrial fibrillation [361].

EPA and DHA are important for cognitive function throughout the lifespan (reviewed recently [376]). The importance of omega-3 PUFA and DHA in particular in supporting neurological development and function in humans was first established when the inclusion of alpha-linolenic acid (ALA, 18:3n-3) in a total parental nutrition emulsion increased DHA in serum phospholipid and corrected neurological symptoms that had developed during parental nutrition without ALA [377]. In adults, there is evidence that EPA and DHA may support or improve cognitive function but study results are not consistent and appear to be dependent on the type of the cognitive test, baseline cognitive function and dose and timing of EPA + DHA intake [346,376,378]. Low levels of plasma EPA and DHA were first observed in individuals with Alzheimer's disease, other types of dementia and cognitive impairment in 2000 [379] and an association between blood levels of EPA and DHA and dementia has been confirmed [380]. Higher blood DHA (DHA in plasma phosphatidylcholine) has been associated with reduced risk of all-cause dementia in a prospective follow-up study [15]. Intervention trials with EPA and/or DHA in individuals with Alzheimer's disease have typically shown no benefit [381], except in Alzheimer's patients with very mild cognitive dysfunction [382]. A recent meta-analysis has indicated that supplementation with EPA + DHA > 1 g/day can improve immediate recall or episodic memory in individuals with mild memory complaints but not those with no complaints [378]. It also appears that sex of the subject may influence results as women may receive more benefits in episodic memory while men benefit more from reaction time and working memory [383] although body weight differences between sexes might result in different effective dosing of EPA and DHA [384].

Cost-effectiveness assessment for the use of omega-3 PUFA treatment completed using outcomes from the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI) Prevenzione Trial estimated that omega-3 PUFA was cost-effective [385,386] and the cost-effectiveness was similar to other drugs prescribed at the time (simvastatin and pravastatin) [386]. These assessments expanded to other studies and countries for confirmation [387,388]. The GISSI Prevenzione [359] and the GISSI heart failure [389] trials were also used to determine the cost-effectiveness of pharmaceutical grade EPA + DHA in the ethyl ester form [390,391]. EPA + DHA use was also determined to be cost-effective in the treatment of hypertriglyceridemia [392]. More recently the use of EPA only omega-3 supplementation for secondary prevention of cardiovascular disease [393] and reducing the incidence of coronary heart disease in the elderly in Korea [394] have been associated with cost savings. Cost-savings with omega-3 supplementation have also been predicted in populations receiving parental nutrition [395,396] and with perioperative strategies to reduce surgical morbidity in patients with gastrointestinal cancer [397,398]. Although pregnant women were not included in the present analysis, low blood levels of EPA + DHA in pregnant women has been documented [399,400] and a recent econometric analysis also indicated that DHA supplementation of pregnant women could save the Australian public hospital system between 15 and 51 million Australian dollars per year [401].

5.5. The challenge of increasing blood EPA + DHA levels through dietary intakes

It is important to evaluate the feasibility of supplying the world's population with the recommended amounts of EPA and DHA. That is, to determine whether there are adequate sources of EPA and DHA available to support, for example, shifting all countries and regions to the green category, a level of >8% EPA + DHA in their erythrocytes or the equivalent in other blood fractions. The main dietary source of EPA and DHA is fish and other marine foods [8,9,11,402]. Of course, this may be supplied by fortified foods or supplements as well. A recent analysis of omega-3 fatty acid sources has been recently published [347]. It is clear from this and other such analyses that the total fish availability had plateaued by the early 1990's and is inelastic [403]. Aquaculture has steadily increased relative to the wild fish catch but most such species still depend upon dietary fish oil supplementation from the wild catch, and thus the total cannot at present be increased substantially. It was estimated that for the world's population of 7.2 billion people, to supply 500 mg/day of DHA + EPA would require 1.3 million metric tons of EPA + DHA per annum. Human consumption is now approximately 200 thousand metric tons, enough to supply 500 mg/day of EPA + DHA to only 15% of the world's population. In order to raise the world's population into the green range, it was estimated above that 1250 mg/day of EPA + DHA would be required and at this level of intake, a total of 3.12 million metric tons of EPA + DHA would be needed every year. At this higher level of intake, the present production would only support about 6% of the population.

How then might the omega-3 supply be increased to support healthful blood levels of EPA and DHA? One suggestion has been to increase the consumption of ALA, the precursor of EPA and DHA as there is an abundant supply of this fatty acid in vegetable oils. However, the human conversion to EPA is limited and conversion to DHA is very low [404] such that supplementation studies with ALA in humans have shown little increases in EPA and DHA [405]. There is the potential to increase the conversion of ALA to EPA and DHA by reducing the intake of linoleic acid (LA, 18:2n-6) [340]. However, in order to achieve high (>8% in erythrocytes) blood levels of EPA + DHA, total PUFA intake levels would have to be drastically reduced (<2% of total energy) to minimize competition for $\Delta 6$ desaturation [406] and removing omega-6 PUFA would be controversial. This would also have a major impact on the human food supply in regard to seed oil consumption, and as already observed with efforts to remove *trans* fatty acids,

replacing types of fatty acids in the industrial food supply is a challenging and problematic endeavour [407]. The reduction in linoleic acid intake also serves to increase EPA and DHA content of tissues due to a lower competition for incorporation into complex lipids [408]. In any case, preformed sources of EPA and particularly of DHA are required for the human diet to reach high blood levels of EPA + DHA, perhaps in combination with lower linoleic acid intake.

It is certainly possible to increase heterotrophic fermentation of microorganisms such as *Schizochytrium* [409] and other Thraustochytrids [410] to make both EPA and DHA. Although there are economic hurdles for this source vs. fish oils, an economy of scale could significantly lower price and make it more generally accessible [347]. Algal biomass can be used for aquaculture and animal feed rather than the extracted oil, as well, supplying a lower cost but efficacious source of EPA and DHA. Another possible source of EPA and DHA in the near future could be derived from genetically modified oilseed crops such as canola or soybeans [411]. Petrie et al., have estimated that there is an EPA/DHA equivalence of one hectare of *Brassica napus* to 10,000 fish based on an omega-3 content that has already been achieved in lab trials [412]. Although genetically modified food sources are not widely accepted at this time, genome sequences for producing omega-3 LCPUFA have been identified [413]. One could envisage an initial use in animal feed and aquaculture, but also the development of productive EPA + DHA microorganisms such that enriched foods and oils could be generated on a much larger scale in order to potentially supply enough EPA and DHA for the world's population.

6. Concluding remarks

Blood levels of EPA + DHA are variable across the globe, with most of the countries and regions of the world having levels that are considered low to very low. While the global mapping of blood levels of EPA + DHA tend to agree with previous assessments of dietary intake of omega-3 PUFA from seafood [4], blood levels are less error prone and thus blood level targets can be better linked to specific chronic disease outcomes and events. The low and very low bloods levels observed for most of the globe are associated with an increased risk in cardiovascular related mortality based on previous observational studies [13,14]. It is also highly likely that increased blood levels of EPA + DHA across the globe would reduce the risk of cognitive decline with normal aging, but further evidence is needed to identify specific blood level targets [346,376]. It is also clear that data on blood levels of EPA + DHA is needed for large regions of the globe, particularly for developing countries. Efforts to establish reference ranges in blood levels of fatty acids is needed and this data would complement existing information on dietary intake but fatty acid data can also serve as phenotype information for genome wide association studies. Given the challenges of fatty acid analyses and reporting, an international initiative should be considered to lead to standardized approaches and the development of a systematic database.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.plipres.2016.05.001>.

Conflicts of interest

Financial support for this review was provided by DSM Nutritional Products and Norman Salem, Jr. is employed by DSM, a manufacturer of omega-3 fatty acids.

Acknowledgments

The authors would like to dedicate this manuscript to co-author Mary "Roberta" Higgins who passed away on October 4th, 2015 during the writing stage.

References

- [1] Mendis S, Chestnov O, World HO. Global Status Report on Noncommunicable Diseases 2014. Geneva: World Health Organization; 2014.
- [2] Trikalinos TA, Lee J, Moorthy D, Yu WW, Lau J, Lichtenstein AH, et al. AHRQ Technical Reviews. Effects of Eicosapentaenoic Acid and Docosahexaenoic Acid on Mortality Across Diverse Settings: Systematic Review and Meta-Analysis of Randomized Trials and Prospective Cohorts: Nutritional Research Series. , vol 4Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
- [3] Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. *Evid Rep Technol Assess* 2010;1–727.
- [4] Micha R, Khatibzadeh S, Shi P, Fahimi S, Lim S, Andrews KG, et al. Global, regional, and national consumption levels of dietary fats and oils in 1990 and 2010: a systematic analysis including 266 country-specific nutrition surveys. *BMJ* 2014;348:g2272.
- [5] Patterson AC, Hogg RC, Kishi DM, Stark KD. Biomarker and dietary validation of a Canadian food frequency questionnaire to measure eicosapentaenoic and docosahexaenoic acid intakes from whole food, functional food, and nutraceutical sources. *J Acad Nutr Diet* 2012;112:1005–14.
- [6] Fratesi JA, Hogg RC, Young-Newton GS, Patterson AC, Charkhazarin P, Block Thomas K, et al. Direct quantitation of omega-3 fatty acid intake of Canadian residents of a long-term care facility. *Appl Physiol Nutr Metab=Physiol Appl Nutr Metab* 2009;34:1–9.
- [7] Patterson AC, Metherell AH, Hanning RM, Stark KD. The percentage of DHA in erythrocytes can detect non-adherence to advice to increase EPA and DHA intakes. *Br J Nutr* 2014;111:270–8.
- [8] Block RC, Harris WS, Pottala JV. Determinants of blood cell omega-3 fatty acid content. *Open Biomark J* 2008;1:1–6.
- [9] Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose–response randomized controlled trial. *J Am Heart Assoc* 2013;2:e000513.
- [10] Stark KD, Beblo S, Murthy M, Whitty JE, Buda-Abela M, Janisse J, et al. Alcohol consumption in pregnant, black women is associated with decreased plasma and erythrocyte docosahexaenoic acid. *Alcohol Clin Exp Res* 2005;29:130–40.
- [11] Harris WS, Pottala JV, Lacey SM, Vasani RS, Larson MG, Robins SJ. Clinical correlates and heritability of erythrocyte eicosapentaenoic and docosahexaenoic acid content in the Framingham Heart Study. *Atherosclerosis* 2012;225:425–31.
- [12] Crowe FL, Skeaff CM, Green TJ, Gray AR. Serum n-3 long-chain PUFA differ by sex and age in a population-based survey of New Zealand adolescents and adults. *Br J Nutr* 2008;99:168–74.
- [13] 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. *JAMA* 1995;274:1363–7.
- [14] 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.
- [15] 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.
- [16] Abraham RA, Bahl VK, Parshad R, Seenu V, Roy A, Golandaz S, et al. Content of trans fatty acids in human cheek epithelium: comparison with serum and adipose tissue. *Biomed Res Int* 2013;276174:8.
- [17] Allard JP, Kurian R, Aghdassi E, Muggli R, Royall D. Lipid peroxidation during n-3 fatty acid and vitamin E supplementation in humans. *Lipids* 1997;32:535–41.
- [18] Almendingen K, Hostmark AT, Fausa O, Mosdol A, Aabakken L, Vatn MH. Familial adenomatous polyposis patients have high levels of arachidonic acid and docosahexaenoic acid and low levels of linoleic acid and alpha-linolenic acid in serum phospholipids. *Int J Cancer* 2007;120:632–7.
- [19] Alshatwi AA, Alrefai NA. A comparison of serum omega-3 fatty acid concentrations between patients with coronary heart disease and healthy subjects. *Pak J Nutr* 2007;6:72–4.
- [20] Ambring A, Johansson M, Axelsen M, Gan L, Strandvik B, Friberg P. Mediterranean-inspired diet lowers the ratio of serum phospholipid n-6 to n-3 fatty acids, the number of leukocytes and platelets, and vascular endothelial growth factor in healthy subjects. *Am J Clin Nutr* 2006;83:575–81.
- [21] Amiano P, Dorronsoro M, de Renobales M, de Gordo JC R, Irigoien I. Very-long-chain omega-3 fatty acids as markers for habitual fish intake in a population consuming mainly lean fish: the EPIC cohort of Gipuzkoa. *European Prospective Investigation into Cancer and Nutrition. Eur J Clin Nutr* 2001;55:827–32.
- [22] An WS, Kim SE, Kim KH, Lee S, Park Y, Kim HJ, et al. Comparison of fatty acid contents of erythrocyte membrane in hemodialysis and peritoneal dialysis patients. *J Ren Nutr* 2009;19:267–74.
- [23] Antalics CJ, Stevens LJ, Campbell M, Pazdro R, Ericson K, Burgess JR. Omega-3 fatty acid status in attention-deficit/hyperactivity disorder. *Prostaglandins Leukot Essent Fat Acids* 2006;75:299–308.
- [24] Arterburn LM, Oken HA, Hoffman JP, Bailey-Hall E, Chung G, Rom D, et al. Bioequivalence of docosahexaenoic acid from different algal oils in capsules and in a DHA-fortified food. *Lipids* 2007;42:1011–24.
- [25] Astorg P, Bertrais S, Alessandri JM, Guesnet P, Kesse-Guyot E, Linard A, et al. Long-chain n-3 fatty acid levels in baseline serum phospholipids do not predict later occurrence of depressive episodes: a nested case–control study within a cohort of middle-aged French men and women. *Prostaglandins Leukot Essent Fat Acids* 2009;81:265–71.
- [26] Astorg P, Bertrais S, Laporte F, Arnault N, Estaquio C, Galan P, et al. Plasma n-6 and n-3 polyunsaturated fatty acids as biomarkers of their dietary intakes: a cross-

- sectional study within a cohort of middle-aged French men and women. *Eur J Clin Nutr* 2008;62:1155–61.
- [27] Aupperle RL, Denney DR, Lynch SG, Carlson SE, Sullivan DK. Omega-3 fatty acids and multiple sclerosis: relationship to depression. *J Behav Med* 2008; 31:127–35.
- [28] Austria JA, Richard MN, Chahine MN, Edell AL, Malcolmson LJ, Dupasquier CM, et al. Bioavailability of alpha-linolenic acid in subjects after ingestion of three different forms of flaxseed. *J Am Coll Nutr* 2008;27:214–21.
- [29] Bagdade JD, Ritter MC, Davidson M, Subbiah PV. Effect of marine lipids on cholesteryl ester transfer and lipoprotein composition in patients with hypercholesterolemia. *Arterioscler Thromb J Vasc Biol/Am Heart Assoc* 1992;12:1146–52.
- [30] Baghai TC, Varallo-Bedarida G, Born C, Hafner S, Schule 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.
- [31] Barcelo-Coblijn G, Murphy EJ, Othman R, Moghadasian MH, Kashour T, Friel JK. Flaxseed oil and fish-oil capsule consumption alters human red blood cell n-3 fatty acid composition: a multiple-dosing trial comparing 2 sources of n-3 fatty acid. *Am J Clin Nutr* 2008;88:801–9.
- [32] Barkia A, Mohamed K, Smaoui M, Zouari N, Hammami M, Nasri M. Change of diet, plasma lipids, lipoproteins, and fatty acids during Ramadan: a controversial association of the considered Ramadan model with atherosclerosis risk. *J Health Popul Nutr* 2011;29:486–93.
- [33] Berr C, Akbaraly T, Arnaud J, Hininger I, Roussel AM, Barberger GP. Increased selenium intake in elderly high fish consumers may account for health benefits previously ascribed to omega-3 fatty acids. *J Nutr Health Aging* 2009;13:14–8.
- [34] 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.
- [35] Bloomer RJ, Larson DE, Fisher-Wellman KH, Galpin AJ, Schilling BK. Effect of eicosapentaenoic and docosahexaenoic acid on resting and exercise-induced inflammatory and oxidative stress biomarkers: a randomized, placebo controlled, cross-over study. *Lipids Health Dis* 2009;8:36.
- [36] Bonna KH, Bjerve KS, Nordoy A. Docosahexaenoic and eicosapentaenoic acids in plasma phospholipids are divergently associated with high density lipoprotein in humans. *Arterioscler Thromb J Vasc Biol/Am Heart Assoc* 1992;12:675–81.
- [37] Brasky TM, Till C, White E, Neuhouser ML, Song X, Goodman P, et al. Serum phospholipid fatty acids and prostate cancer risk: results from the prostate cancer prevention trial. *Am J Epidemiol* 2011;173:1429–39.
- [38] Brignardello J, Morales P, Diaz E, Brunser O, Gotteland M. Increase of plasma fatty acids without changes in n-6/n-3-PUFA ratio in asymptomatic obese subjects. *Arch Latinoam Nutr* 2011;61:149–53.
- [39] Brown AJ, Pang E, Roberts DC. Erythrocyte eicosapentaenoic acid versus docosahexaenoic acid as a marker for fish and fish oil consumption. *Prostaglandins Leukot Essent Fat Acids* 1991;44:103–6.
- [40] Brox J, Olaussen K, Osterud B, Elvevoll EO, Bjornstad E, Brattebog G, et al. A long-term seal- and cod-liver-oil supplementation in hypercholesterolemic subjects. *Lipids* 2001;36:7–13.
- [41] Brude IR, Drevon CA, Hjermann I, Seljeflot I, Lund-Katz S, Saarem K, et al. Peroxidation of LDL from combined-hyperlipidemic male smokers supplied with omega-3 fatty acids and antioxidants. *Arterioscler Thromb Vasc Biol* 1997;17:2576–88.
- [42] Cao J, Schwichtenberg KA, Hanson NQ, Tsai MY. Incorporation and clearance of omega-3 fatty acids in erythrocyte membranes and plasma phospholipids. *Clin Chem* 2006;52:2265–72.
- [43] Carrero JJ, Baro L, Fonolla J, Gonzalez-Santiago M, Martinez-Ferez A, Castillo R, et al. Cardiovascular effects of milk enriched with omega-3 polyunsaturated fatty acids, oleic acid, folic acid, and vitamins E and B6 in volunteers with mild hyperlipidemia. *Nutrition*, 20. Los Angeles County, Calif: Burbank; 2004 521–7.
- [44] Caspar-Bauguil S, Garcia J, Galinier A, Periquet B, Ferrieres J, Allenbach S, et al. Positive impact of long-term lifestyle change on erythrocyte fatty acid profile after acute coronary syndromes. *Arch Cardiovasc Dis* 2010;103:106–14.
- [45] Caspar-Bauguil S, Montastier E, Galinon F, Frisch-Benarous D, Salvayre R, Ritz P. Anorexia nervosa patients display a deficit in membrane long chain poly-unsaturated fatty acids. *Clin Nutr (Edinburgh, Scotland)* 2012;31:386–90.
- [46] Cazzola R, Rondanelli M, Russo-Volpe S, Ferrari E, Cestaro B. Decreased membrane fluidity and altered susceptibility to peroxidation and lipid composition in overweight and obese female erythrocytes. *J Lipid Res* 2004;45:1846–51.
- [47] Cederholm TE, Berg AB, Johansson EK, Hellstrom KH, Palmblad JE. Low levels of essential fatty acids are related to impaired delayed skin hypersensitivity in malnourished chronically ill elderly people. *Eur J Clin Invest* 1994;24:615–20.
- [48] Cherubini A, Andres-Lacueva C, Martin A, Lauretani F, Iorio AD, Bartali B, et al. Low plasma N-3 fatty acids and dementia in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 2007;62:1120–6.
- [49] Chien KL, Chao CL, Kuo CH, Lin HJ, Liu PH, Chen PR, et al. Plasma fatty acids and the risk of metabolic syndrome in ethnic Chinese adults in Taiwan. *Lipids Health Dis* 2011;10:33.
- [50] Coates AM, Sioutis S, Buckley JD, Howe PR. Regular consumption of n-3 fatty acid-enriched pork modifies cardiovascular risk factors. *Br J Nutr* 2009;101:592–7.
- [51] Conklin SM, Harris JL, Manuck SB, Yao JK, Hibbeln JR, Muldoon MF. Serum omega-3 fatty acids are associated with variation in mood, personality and behavior in hypercholesterolemic community volunteers. *Psychiatry Res* 2007;152:1–10.
- [52] Conquer JA, Cheryk LA, Chan E, Gentry PA, Holub BJ. Effect of supplementation with dietary seal oil on selected cardiovascular risk factors and hemostatic variables in healthy male subjects. *Thromb Res* 1999;96:239–50.
- [53] Conquer JA, Holub BJ. Supplementation with an algae source of docosahexaenoic acid increases (n-3) fatty acid status and alters selected risk factors for heart disease in vegetarian subjects. *J Nutr* 1996;126:3032–9.
- [54] Conquer JA, Roelfsema H, Zecevic J, Graham TE, Holub BJ. Effect of exercise on FA profiles in n-3 FA-supplemented and -nonsupplemented premenopausal women. *Lipids* 2002;37:947–51.
- [55] Crispin SP, Geelen A, Souverein OW, Hulshof PJ, Ruprich J, Dofkova M, et al. Biomarker-based evaluation of two 24-h recalls for comparing usual fish, fruit and vegetable intakes across European centers in the EFCOVAL Study. *Eur J Clin Nutr* 2011;65(Suppl. 1):S38–47.
- [56] Crowe FL, Skeaff CM, Green TJ, Gray AR. Serum phospholipid n 3 long-chain polyunsaturated fatty acids and physical and mental health in a population-based survey of New Zealand adolescents and adults. *Am J Clin Nutr* 2007;86:1278–85.
- [57] Cunnane SC, Hamadeh MJ, Liede AC, Thompson LU, Wolever TM, Jenkins DJ. Nutritional attributes of traditional flaxseed in healthy young adults. *Am J Clin Nutr* 1995;61:62–8.
- [58] Cunnane SC, Schneider JA, Tangney C, Tremblay-Mercier J, Fortier M, Bennett DA, et al. Plasma and brain fatty acid profiles in mild cognitive impairment and Alzheimer's disease. *J Alzheimers Dis* 2012;29:691–7.
- [59] Dahl L, Maeland CA, Bjorkkjaer T. A short food frequency questionnaire to assess intake of seafood and n-3 supplements: validation with biomarkers. *Nutr J* 2011;10:127.
- [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] Dawczynski C, Martin L, Wagner A, Jahreis G. n-3 LC-PUFA-enriched dairy products are able to reduce cardiovascular risk factors: a double-blind, cross-over study. *Clin Nutr (Edinburgh, Scotland)* 2010;29:592–9.
- [62] de Groot RH, Hornstra G, Jolles J. Exploratory study into the relation between plasma phospholipid fatty acid status and cognitive performance. *Prostaglandins Leukot Essent Fat Acids* 2007;76:165–72.
- [63] de Groot RH, van Boxtel MP, Schiepers OJ, Hornstra G, Jolles J. Age dependence of plasma phospholipid fatty acid levels: potential role of linoleic acid in the age-associated increase in docosahexaenoic acid and eicosapentaenoic acid concentrations. *Br J Nutr* 2009;102:1058–64.
- [64] De Groot G, De Laporte A, Dhondt G, Christophe A. Improvement in the plasma omega-3 index by the use of a fish oil-enriched spread. *Ann Nutr Metab* 2008; 53:23–8.
- [65] de Oliveira Otto MC, Wu JH, Baylin A, Vaidya D, Rich SS, Tsai MY, et al. Circulating and dietary omega-3 and omega-6 polyunsaturated fatty acids and incidence of CVD in the Multi-Ethnic Study of Atherosclerosis. *J Am Heart Assoc* 2013;2:000506.
- [66] Delyfer MN, Buaud B, Korobelnik JF, Rougier MB, Schalch W, Etheve S, et al. Association of macular pigment density with plasma omega-3 fatty acids: the PIMAVOSA study. *Investig Ophthalmol Vis Sci* 2012;53:1204–10.
- [67] Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ. Cardiovascular disease risk factors and n-3 fatty acid status in the adult population of James Bay Cree. *Am J Clin Nutr* 2002;76:85–92.
- [68] Dewailly E, Chateau-Degat L, Suhas E. Fish consumption and health in French Polynesia. *Asia Pac J Clin Nutr* 2008;17:86–93.
- [69] Dewailly EE, Blanchet C, Gingras S, Lemieux S, Sauve L, Bergeron J, et al. Relations between n-3 fatty acid status and cardiovascular disease risk factors among Quebecers. *Am J Clin Nutr* 2001;74:603–11.
- [70] Di Stasi D, Bernasconi R, Marchioli R, Marfisi RM, Rossi G, Tognoni G, et al. Early modifications of fatty acid composition in plasma phospholipids, platelets and mononucleates of healthy volunteers after low doses of n-3 polyunsaturated fatty acids. *Eur J Clin Pharmacol* 2004;60:183–90.
- [71] Dodin S, Cunnane SC, Masse B, Lemay A, Jacques H, Asselin G, et al. Flaxseed on cardiovascular disease markers in healthy menopausal women: a randomized, double-blind, placebo-controlled trial. *Nutrition*, 24. Los Angeles County, Calif: Burbank; 2008 23–30.
- [72] Duricic I, Sobajic S, Perunic-Pekovic G, Stojanov M, Rasic Z. Consumption of fish oil supplement alters erythrocyte fatty acid composition in overweight, hypercholesterolemic, middle-aged Serbians. *Nutr Res (N Y, NY)* 2007;27: 529–34.
- [73] 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.
- [74] Edwards R, Peet M, Shay J, Horrobin D. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* 1998;48:149–55.
- [75] Elizondo A, Araya J, Rodrigo R, Poniachik J, Csendes A, Maluenda F, et al. Polyunsaturated fatty acid pattern in liver and erythrocyte phospholipids from obese patients. *Obesity* 2007;15:24–31.
- [76] Emanuele E, Brondino N, Re S, Bertona M, Geroldi D. Serum omega-3 fatty acids are associated with ultimatum bargaining behavior. *Physiol Behav* 2009;96: 180–3.
- [77] Feart C, Peuchant E, Letenneur L, Samieri C, Montagnier D, Fourrier-Reglat A, et al. Plasma eicosapentaenoic acid is inversely associated with severity of depressive symptomatology in the elderly: data from the Bordeaux sample of the Three-City Study. *Am J Clin Nutr* 2008;87:1156–62.
- [78] Fernandez-Real JM, Broch M, Vendrell J, Ricart W. Insulin resistance, inflammation, and serum fatty acid composition. *Diabetes Care* 2003;26:1362–8.
- [79] Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab* 2006;91:439–46.

- [80] Fillion M, Lemire M, Philibert A, Frenette B, Weiler HA, Deguire JR, et al. Visual acuity in fish consumers of the Brazilian Amazon: risks and benefits from local diet. *Public Health Nutr* 2011;14:2236–44.
- [81] Fortier M, Tremblay-Mercier J, Plourde M, Chouinard-Watkins R, Vandal M, Pifferi F, et al. Higher plasma n-3 fatty acid status in the moderately healthy elderly in southern Quebec: higher fish intake or aging-related change in n-3 fatty acid metabolism? *Prostaglandins Leukot Essent Fat Acids* 2010;82:277–80.
- [82] Freije A. Fatty acid profile of the erythrocyte membranes of healthy Bahraini citizens in comparison with coronary heart disease patients. *J Oleo Sci* 2009;58:379–88.
- [83] Garneau V, Rudkowska I, Paradis AM, Godin G, Julien P, Perusse L, et al. Omega-3 fatty acids status in human subjects estimated using a food frequency questionnaire and plasma phospholipids levels. *Nutr J* 2012;11:46.
- [84] Geppert J, Demmelmair H, Hornstra G, Koletzko B. Co-supplementation of healthy women with fish oil and evening primrose oil increases plasma docosahexaenoic acid, gamma-linolenic acid and dihomo-gamma-linolenic acid levels without reducing arachidonic acid concentrations. *Br J Nutr* 2008;99:360–9.
- [85] Geppert J, Kraft V, Demmelmair H, Koletzko B. Docosahexaenoic acid supplementation in vegetarians effectively increases omega-3 index: a randomized trial. *Lipids* 2005;40:807–14.
- [86] Gerasimova E, Perova N, Ozerova I, Polessky V, Metelskaya V, Sherbakova I, et al. The effect of dietary n-3 polyunsaturated fatty acids on HDL cholesterol in Chukot residents vs muscovites. *Lipids* 1991;26:261–5.
- [87] Glew RH, Chuang LT, Berry T, Okolie H, Crossey MJ, Vanderjagt DJ. Lipid profiles and trans fatty acids in serum phospholipids of semi-nomadic Fulani in northern Nigeria. *J Health Popul Nutr* 2010;28:159–66.
- [88] Gong J, Rosner B, Rees DG, Berson EL, Weigel-DiFranco CA, Schaefer EJ. Plasma docosahexaenoic acid levels in various genetic forms of retinitis pigmentosa. *Investig Ophthalmol Vis Sci* 1992;33:2596–602.
- [89] Green P, Hermesh H, Monselise A, Marom S, Presburger G, Weizman A. Red cell membrane omega-3 fatty acids are decreased in nondepressed patients with social anxiety disorder. *Eur Neuropsychopharmacol* 2006;16:107–13.
- [90] Gronn M, Gorbitz C, Christensen E, Levorsen A, Ose L, Hagve TA, et al. Dietary n-6 fatty acids inhibit the incorporation of dietary n-3 fatty acids in thrombocyte and serum phospholipids in humans: a controlled dietetic study. *Scand J Clin Lab Invest* 1991;51:255–63.
- [91] Grundt H, Nilsen DW, Hetland O, Aarsland T, Baksaas I, Grande T, et al. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. *J Intern Med* 1995;237:249–59.
- [92] Guarini P, Stanzial AM, Olivieri O, Casaril M, Galvani S, Pantalena M, et al. Erythrocyte membrane lipids and serum selenium in post-viral and alcoholic cirrhosis. *Clin Chim Acta* 1998;270:139–50.
- [93] Gustafsson IB, Vessby B, Ohrvall M, Nydahl M. A diet rich in monounsaturated rapeseed oil reduces the lipoprotein cholesterol concentration and increases the relative content of n-3 fatty acids in serum in hyperlipidemic subjects. *Am J Clin Nutr* 1994;59:667–74.
- [94] Hall MN, Campos H, Li H, Sesso HD, Stampfer MJ, Willett WC, et al. Blood levels of long-chain polyunsaturated fatty acids, aspirin, and the risk of colorectal cancer. *Cancer Epidemiol Biomark Prev* 2007;16:314–21.
- [95] Hamazaki K, Itomura M, Sawazaki S, Hamazaki T. Fish oil reduces tooth loss mainly through its anti-inflammatory effects? *Med Hypotheses* 2006;67:868–70.
- [96] Hamazaki-Fujita N, Hamazaki K, Tohno H, Itomura M, Terashima Y, Hamazaki T, et al. Polyunsaturated fatty acids and blood circulation in the forearm during a mental arithmetic task. *Brain Res* 2011;1397:38–45.
- [97] Harper CR, Edwards MJ, DeFillippis AP, Jacobson TA. Flaxseed oil increases the plasma concentrations of cardioprotective (n-3) fatty acids in humans. *J Nutr* 2006;136:83–7.
- [98] Harris JL, Hibbeln JR, Mackey RH, Muldoon MF. Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients. *Prostaglandins Leukot Essent Fat Acids* 2004;71:263–9.
- [99] Harris WS, Lemke SL, Hansen SN, Goldstein DA, DiRienzo MA, Su H, et al. Stearidonic acid-enriched soybean oil increased the omega-3 index, an emerging cardiovascular risk marker. *Lipids* 2008;43:805–11.
- [100] Harris WS, Pottala JV, Sands SA, Jones PG. Comparison of the effects of fish and fish-oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids. *Am J Clin Nutr* 2007;86:1621–5.
- [101] Harris WS, Pottala JV, Vasan RS, Larson MG, Robins SJ. Changes in erythrocyte membrane trans and marine fatty acids between 1999 and 2006 in older Americans. *J Nutr* 2012;142:1297–303.
- [102] Harris WS, Reid KJ, Sands SA, Spertus JA. Blood omega-3 and trans fatty acids in middle-aged acute coronary syndrome patients. *Am J Cardiol* 2007;99:154–8.
- [103] Harvei S, Bjerve KS, Tretli S, Jellum E, Robsahm TE, Vatten L. Prediagnostic level of fatty acids in serum phospholipids: omega-3 and omega-6 fatty acids and the risk of prostate cancer. *Int J Cancer* 1997;71:545–51.
- [104] Haug A, Nyquist NF, Mosti TJ, Andersen M, Hostmark AT. Increased EPA levels in serum phospholipids of humans after four weeks daily ingestion of one portion chicken fed linseed and rapeseed oil. *Lipids Health Dis* 2012;11:104.
- [105] Heude B, Ducimetiere P, Berr C. Cognitive decline and fatty acid composition of erythrocyte membranes—the EVA study. *Am J Clin Nutr* 2003;77:803–8.
- [106] Hibbeln JR, Linnoila M, Umhau JC, Rawlings R, George DT, Salem Jr N. Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biol Psychiatry* 1998;44:235–42.
- [107] High KP, Sinclair J, Easter LH, Case D, Chilton FH. Advanced age, but not energy, is associated with altered serum polyunsaturated fatty acid levels. *J Nutr Health Aging* 2003;7:378–84.
- [108] Hirai K, Horiuchi R, Ohno Y, Higuchi H, Asano Y. Lower eicosapentaenoic acid and higher arachidonic acid levels in sera of young adults in the Netherlands than in Japan. *Environ Health Prev Med* 2000;5:60–5.
- [109] Hjartaker A, Lund E, Bjerve KS. Serum phospholipid fatty acid composition and habitual intake of marine foods registered by a semi-quantitative food frequency questionnaire. *Eur J Clin Nutr* 1997;51:736–42.
- [110] Hlavaty P, Kunesova M, Gojova M, Tvrzicka E, Vecka M, Roubal P, et al. Change in fatty acid composition of serum lipids in obese females after short-term weight-reducing regimen with the addition of n-3 long chain polyunsaturated fatty acids in comparison to controls. *Physiol Res/Acad Sci Bohemoslov* 2008;57(Suppl. 1):S57–65.
- [111] Hodge AM, Simpson JA, Gibson RA, Sinclair AJ, Makrides M, O'Dea K, et al. Plasma phospholipid fatty acid composition as a biomarker of habitual dietary fat intake in an ethnically diverse cohort. *Nutr Metab Cardiovasc Dis* 2007;17:415–26.
- [112] Hodge J, Sanders K, Sinclair AJ. Differential utilization of eicosapentaenoic acid and docosahexaenoic acid in human plasma. *Lipids* 1993;28:525–31.
- [113] Hoffman DR, Uauy R, Birch DG. Red blood cell fatty acid levels in patients with autosomal dominant retinitis pigmentosa. *Exp Eye Res* 1993;57:359–68.
- [114] Hojo N, Fukushima T, Isoabe A, Gao T, Shiwaku K, Ishida K, et al. Effect of serum fatty acid composition on coronary atherosclerosis in Japan. *Int J Cardiol* 1998;66:31–8.
- [115] Huan M, Hamazaki K, Sun Y, Itomura M, Liu H, Kang W, et al. Suicide attempt and n-3 fatty acid levels in red blood cells: a case control study in China. *Biol Psychiatry* 2004;56:490–6.
- [116] Huang T, Shou T, Cai N, Wahlqvist ML, Li D. Associations of plasma n-3 polyunsaturated fatty acids with blood pressure and cardiovascular risk factors among Chinese. *Int J Food Sci Nutr* 2012;63:667–73.
- [117] Ikeya Y, Fukuyama N, Kitajima W, Ogushi Y, Mori H. Comparison of Eicosapentaenoic Acid Concentrations in Plasma Between Patients with Ischemic Stroke and Control Subjects. *Nutrition*, 29. Los Angeles County, Calif: Burbank; 2013 127–31.
- [118] Imre SG, Fekete I, Farkas T. Increased proportion of docosahexaenoic acid and high lipid peroxidation capacity in erythrocytes of stroke patients. *Stroke J Cereb Circ* 1994;25:2416–20.
- [119] Itakura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, et al. Relationships between plasma fatty acid composition and coronary artery disease. *J Atheroscler Thromb* 2011;18:99–107.
- [120] Ito Y, Shimizu H, Yoshimura T, Ross RK, Kabuto M, Takatsuka N, et al. Serum concentrations of carotenoids, alpha-tocopherol, fatty acids, and lipid peroxides among Japanese in Japan, and Japanese and Caucasians in the US. *Int J Vitam Nutr Res* 1999;69:385–95.
- [121] Itomura M, Fujioka S, Hamazaki K, Kobayashi K, Nagasawa T, Sawazaki S, et al. Factors influencing EPA + DHA levels in red blood cells in Japan. *In vivo* 2008;22:131–5 Athens, Greece.
- [122] Iusupova IU. The fatty acid composition of the phospholipids of the erythrocyte membranes, thrombocytes and alpha-lipoproteins in schizophrenia patients. *Zh Nevropatol Psikhiatr Im S S Korsakova* 1995;95:58–62.
- [123] Jabbar R, Saldeen T. A new predictor of risk for sudden cardiac death. *Ups J Med Sci* 2006;111:169–77.
- [124] James MJ, Ursin VM, Cleland LG. Metabolism of stearidonic acid in human subjects: comparison with the metabolism of other n-3 fatty acids. *Am J Clin Nutr* 2003;77:1140–5.
- [125] Johnson EJ, Chung HY, Caldarella SM, Snodderly DM. The influence of supplemental lutein and docosahexaenoic acid on serum, lipoproteins, and macular pigmentation. *Am J Clin Nutr* 2008;87:1521–9.
- [126] Junshi C, TC C, Junyao L, Peto R, editors. Diet, lifestyle, and mortality in China: a study of the characteristics of 65 Chinese counties. Oxford University Press; 1990.
- [127] Kale A, Joshi S, Naphade N, Sapkale S, Raju MS, Pillai A, et al. Opposite changes in predominantly docosahexaenoic acid (DHA) in cerebrospinal fluid and red blood cells from never-medicated first-episode psychotic patients. *Schizophr Res* 2008;98:295–301.
- [128] Kalogeropoulos N, Panagiotakos DB, Pitsavos C, Chrysoshoou C, Rousinou G, Toutouza M, et al. Unsaturated fatty acids are inversely associated and n-6/n-3 ratios are positively related to inflammation and coagulation markers in plasma of apparently healthy adults. *Clin Chim Acta* 2010;411:584–91.
- [129] Karlsson J, Lindh G, Ronnebergh TR. Smoking, plasma antioxidants and essential fatty acids before and after nutritional therapy. *Can J Cardiol* 1996;12:665–70.
- [130] Kawabata T, Hirota S, Hirayama T, Adachi N, Hagiwara C, Iwama N, et al. Age-related changes of dietary intake and blood eicosapentaenoic acid, docosahexaenoic acid, and arachidonic acid levels in Japanese men and women. *Prostaglandins Leukot Essent Fat Acids* 2011;84:131–7.
- [131] Keenan AH, Pedersen TL, Fillaus K, Larson MK, Shearer GC, Newman JW. Basal omega-3 fatty acid status affects fatty acid and oxylipin responses to high-dose n-3-HUFA in healthy volunteers. *J Lipid Res* 2012;53:1662–9.
- [132] Kelley DS, Siegel D, Vemuri M, Chung GH, Mackey BE. Docosahexaenoic acid supplementation decreases remnant-like particle-cholesterol and increases the (n-3) index in hypertriglyceridemic men. *J Nutr* 2008;138:30–5.
- [133] Kew S, Mesa MD, Tricon S, Buckley R, Minihiang AM, Yaqoob P. Effects of oils rich in eicosapentaenoic and docosahexaenoic acids on immune cell composition and function in healthy humans. *Am J Clin Nutr* 2004;79:674–81.
- [134] Khanaki K, Nouri M, Ardekani AM, Ghassemzadeh A, Shahnaizi V, Sadeghi MR, et al. Evaluation of the relationship between endometriosis and omega-3 and omega-6 polyunsaturated fatty acids. *Iran Biomed J* 2012;16:38–43.

- [135] Kibayashi E, Zhang M, Liu ZY, Sekine M, Sokejima S, Kagamimori S. Comparative studies on serum taurine and plasma fatty acids in humans between the sea side area in Toyama, Japan and the mountain areas in Inner Mongolia, China. *Adv Exp Med Biol* 2000;483:143–8.
- [136] Kim YJ, Kim OY, Cho Y, Chung JH, Jung YS, Hwang GS, et al. Plasma phospholipid fatty acid composition in ischemic stroke: importance of docosahexaenoic acid in the risk for intracranial atherosclerotic stenosis. *Atherosclerosis* 2012;225:418–24.
- [137] Kitayama A, Arisawa K, Uemura H, Hiyoshi M, Takami H, Sawachika F, et al. Correlations of fish intake and plasma docosahexaenoic acid levels with each congener of PCDDs/PCDFs/dioxin-like PCBs in blood from the Japanese population. *Int Arch Occup Environ Health* 2011;84:927–35.
- [138] Knoll N, Kuhn K, Kyallo FM, Kiage-Mokua BN, Jahreis G. High content of long-chain n-3 polyunsaturated fatty acids in red blood cells of Kenyan Maasai despite low dietary intake. *Lipids Health Dis* 2011;10:141.
- [139] Kobayashi M, Sasaki S, Kawabata T, Hasegawa K, Akabane M, Tsugane S. Single measurement of serum phospholipid fatty acid as a biomarker of specific fatty acid intake in middle-aged Japanese men. *Eur J Clin Nutr* 2001;55:643–50.
- [140] Konagai C, Yanagimoto K, Hayamizu K, Han L, Tsuji T, Koga Y. Effects of krill oil containing n-3 polyunsaturated fatty acids in phospholipid form on human brain function: a randomized controlled trial in healthy elderly volunteers. *Clin Interv Aging* 2013;8:1247–57.
- [141] Kondo K, Morino K, Nishio Y, Kondo M, Fuke T, Ugi S, et al. Effects of a fish-based diet on the serum adiponectin concentration in young, non-obese, healthy Japanese subjects. *J Atheroscler Thromb* 2010;17:628–37.
- [142] Kroger E, Verreault R, Carmichael PH, Lindsay J, Julien P, Dewailly E, et al. Omega-3 fatty acids and risk of dementia: the Canadian Study of Health and Aging. *Am J Clin Nutr* 2009;90:184–92.
- [143] Kroger J, Zietemann V, Enzenbach C, Weikert C, Jansen EH, Doring F, et al. Erythrocyte membrane phospholipid fatty acids, desaturase activity, and dietary fatty acids in relation to risk of type 2 diabetes in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. *Am J Clin Nutr* 2011;93:127–42.
- [144] Kuriki K, Nagaya T, Tokudome Y, Imaeda N, Fujiwara N, Sato J, et al. Plasma concentrations of (n-3) highly unsaturated fatty acids are good biomarkers of relative dietary fatty acid intakes: a cross-sectional study. *J Nutr* 2003;133:3643–50.
- [145] Kuriki K, Wakai K, Hirose K, Matsuo K, Ito H, Suzuki T, et al. Risk of colorectal cancer is linked to erythrocyte compositions of fatty acids as biomarkers for dietary intakes of fish, fat, and fatty acids. *Cancer Epidemiol Biomark Prev* 2006;15:1791–8.
- [146] Kuriki K, Wakai K, Matsuo K, Hiraki A, Suzuki T, Yamamura Y, et al. Gastric cancer risk and erythrocyte composition of docosahexaenoic acid with anti-inflammatory effects. *Cancer Epidemiol Biomark Prev* 2007;16:2406–15.
- [147] Kuroki F, Iida M, Matsumoto T, Aoyagi K, Kanamoto K, Fujishima M. Serum n3 polyunsaturated fatty acids are depleted in Crohn's disease. *Dig Dis Sci* 1997;42:1137–41.
- [148] Kurotani K, Sato M, Ejima Y, Nanri A, Yi S, Pham NM, et al. High levels of stearic acid, palmitoleic acid, and dihomo-gamma-linolenic acid and low levels of linoleic acid in serum cholesterol ester are associated with high insulin resistance. *Nutr Res (N Y, NY)* 2012;32:669–75 e3.
- [149] Kusumoto A, Ishikura Y, Kawashima H, Kiso Y, Takai S, Miyazaki M. Effects of arachidonate-enriched triacylglycerol supplementation on serum fatty acids and platelet aggregation in healthy male subjects with a fish diet. *Br J Nutr* 2007;98:626–35.
- [150] Laasonen M, Hokkanen L, Leppamaki S, Tani P, Erkkila AT. Project DyAdd: fatty acids and cognition in adults with dyslexia, ADHD, or both. *Prostaglandins Leukot Essent Fat Acids* 2009;81:79–88.
- [151] Ladesich JB, Pottala JV, Romaker A, Harris WS. Membrane level of omega-3 docosahexaenoic acid is associated with severity of obstructive sleep apnea. *J Clin Sleep Med* 2011;7:391–6.
- [152] Lauretani F, Bandinelli S, Bartali B, Cherubini A, Iorio AD, Ble A, et al. Omega-6 and omega-3 fatty acids predict accelerated decline of peripheral nerve function in older persons. *Eur J Neurol* 2007;14:801–8.
- [153] Laurin D, Verreault R, Lindsay J, Dewailly E, Holub BJ. Omega-3 fatty acids and risk of cognitive impairment and dementia. *J Alzheimers Dis* 2003;5:315–22.
- [154] Lauritzen L, Harslof LB, Hellgren LI, Pedersen MH, Molgaard C, Michaelsen KF. Fish intake, erythrocyte n-3 fatty acid status and metabolic health in Danish adolescent girls and boys. *Br J Nutr* 2012;107:697–704.
- [155] Lee HY, Woo J, Chen ZY, Leung SF, Peng XH. Serum fatty acid, lipid profile and dietary intake of Hong Kong Chinese omnivores and vegetarians. *Eur J Clin Nutr* 2000;54:768–73.
- [156] Leeson CP, Mann A, Kattenhorn M, Deanfield JE, Lucas A, Muller DP. Relationship between circulating n-3 fatty acid concentrations and endothelial function in early adulthood. *Eur Heart J* 2002;23:216–22.
- [157] Legrand P, Schmitt B, Mourtou J, Catheline D, Chesneau G, Mireaux M, et al. The consumption of food products from linseed-fed animals maintains erythrocyte omega-3 fatty acids in obese humans. *Lipids* 2010;45:11–9.
- [158] Lemaitre RN, Siscovick DS, Berry EM, Kark JD, Friedlander Y. Familial aggregation of red blood cell membrane fatty acid composition: the Kibbutzim Family Study. *Metab Clin Exp* 2008;57:662–8.
- [159] Lemke SL, Vicini JL, Su H, Goldstein DA, Nemeth MA, Krul ES, et al. Dietary intake of stearidonic acid-enriched soybean oil increases the omega-3 index: randomized, double-blind clinical study of efficacy and safety. *Am J Clin Nutr* 2010;92:766–75.
- [160] Leng GC, Horrobin DF, Fowkes FG, Smith FB, Lowe GD, Donnan PT, et al. Plasma essential fatty acids, cigarette smoking, and dietary antioxidants in peripheral arterial disease. A population-based case-control study. *Arterioscler Thromb; J Vasc Biol/Am Heart Assoc* 1994;14:471–8.
- [161] Leng GC, Taylor GS, Lee AJ, Fowkes FG, Horrobin D. Essential fatty acids and cardiovascular disease: the Edinburgh Artery Study. *Vasc Med* 1999;4:219–26 London, England.
- [162] Lewis MD, Hibbeln JR, Johnson JE, Lin YH, Hyun DY, Loewke JD. Suicide deaths of active-duty US military and omega-3 fatty-acid status: a case-control comparison. *J Clin Psychiatry* 2011;72:1585–90.
- [163] Lindberg M, Midthjell K, Bjerve KS. Long-term tracking of plasma phospholipid fatty acid concentrations and their correlation with the dietary intake of marine foods in newly diagnosed diabetic patients: results from a follow-up of the HUNT Study, Norway. *Br J Nutr* 2013;109:1123–34.
- [164] Lindqvist HM, Sandberg AS, Fagerberg B, Hulthe J. Plasma phospholipid EPA and DHA in relation to atherosclerosis in 61-year-old men. *Atherosclerosis* 2009;205:574–8.
- [165] Liou YA, King DJ, Zibrik D, Innis SM. Decreasing linoleic acid with constant alpha-linolenic acid in dietary fats increases (n-3) eicosapentaenoic acid in plasma phospholipids in healthy men. *J Nutr* 2007;137:945–52.
- [166] Liu JC, Conklin SM, Manuck SB, Yao JK, Muldoon MF. Long-chain omega-3 fatty acids and blood pressure. *Am J Hypertens* 2011;24:1121–6.
- [167] Liu Z, Wang D, Xue Q, Chen J, Li Y, Bai X, et al. Determination of fatty acid levels in erythrocyte membranes of patients with chronic fatigue syndrome. *Nutr Neurosci* 2003;6:389–92.
- [168] Lopez LB, Kritz-Silverstein D, Barrett CE. 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.
- [169] Lucas M, Asselin G, Merette C, Poulin MJ, Dodin S. Validation of an FFQ for evaluation of EPA and DHA intake. *Public Health Nutr* 2009;12:1783–90.
- [170] Lucas M, Dewailly E, Blanchet C, Gingras S, Holub BJ. Plasma omega-3 and psychological distress among Nunavik Inuit (Canada). *Psychiatry Res* 2009;167:266–78.
- [171] Lucas M, Dewailly E, Blanchet C, Gingras S, Holub BJ. Plasma n-3 fatty acids and psychological distress in aboriginal Cree Indians (Canada). *Public Health Nutr* 2009;12:2343–51.
- [172] Lucas M, Kirmayer LJ, Dery S, Dewailly E. Erythrocyte n-3 is inversely correlated with serious psychological distress among the Inuit: data from the Nunavik health survey. *J Am Coll Nutr* 2010;29:211–21.
- [173] Madsen T, Christensen JH, Svensson M, Witt PM, Toft E, Schmidt EB. Marine n-3 polyunsaturated fatty acids in patients with end-stage renal failure and in subjects without kidney disease: a comparative study. *J Ren Nutr* 2011;21:169–75.
- [174] Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Lowered omega-3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res* 1999;85:275–91.
- [175] Magnusdottir AR, Steingrimsdottir L, Thorgeirsdottir H, Gunnlaugsson G, Skuladottir GV. Docosahexaenoic acid in red blood cells of women of reproductive age is positively associated with oral contraceptive use and physical activity. *Prostaglandins Leukot Essent Fat Acids* 2009;80:27–32.
- [176] Makhoul Z, Kristal AR, Gulati R, Luick B, Bersamin A, O'Brien D, et al. Associations of obesity with triglycerides and C-reactive protein are attenuated in adults with high red blood cell eicosapentaenoic and docosahexaenoic acids. *Eur J Clin Nutr* 2011;65:808–17.
- [177] Maki KC, Reeves MS, Farmer M, Griinari M, Berge K, Vik H, et al. Krill oil supplementation increases plasma concentrations of eicosapentaenoic and docosahexaenoic acids in overweight and obese men and women. *Nutr Res (N Y, NY)* 2009;29:609–15.
- [178] Manav M, Su J, Hughes K, Lee HP, Ong CN. Omega-3 fatty acids and selenium as coronary heart disease risk modifying factors in Asian Indian and Chinese males. *Nutrition*, 20. Los Angeles County, Calif: Burbank; 2004 967–73.
- [179] Mantzioris E, Cleland LG, Gibson RA, Neumann MA, Demasi M, James MJ. Biochemical effects of a diet containing foods enriched with n-3 fatty acids. *Am J Clin Nutr* 2000;72:42–8.
- [180] Marangoni F, Colombo C, Martiello A, Poli A, Paoletti R, Galli C. Levels of the n-3 fatty acid eicosapentaenoic acid in addition to those of alpha linolenic acid are significantly raised in blood lipids by the intake of four walnuts a day in humans. *Nutr Metab Cardiovasc Dis* 2007;457–61.
- [181] Masson S, Marchioli R, Mozaffarian D, Bernasconi R, Milani V, Dragani L, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. *Am Heart J* 2013;165:208–15 e4.
- [182] Mayneris-Perxachs J, Bondia-Pons I, Serra-Hajem L, Catellote AI, Lopez-Sabater MC. Long-chain n-3 fatty acids and classical cardiovascular disease risk factors among the Catalan population. *Food Chem* 2010;119:54–61.
- [183] McAfee AJ, McSorley EM, Cuskelly GJ, Fearon AM, Moss BW, Beattie JA, et al. Red meat from animals offered a grass diet increases plasma and platelet n-3 PUFA in healthy consumers. *Br J Nutr* 2011;105:80–9.
- [184] McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Pandey GN. Selective deficits in erythrocyte docosahexaenoic acid composition in adult patients with bipolar disorder and major depressive disorder. *J Affect Disord* 2010;126:303–11.
- [185] McNaughton SA, Hughes MC, Marks GC. Validation of a FFQ to estimate the intake of PUFA using plasma phospholipid fatty acids and weighed foods records. *Br J Nutr* 2007;97:561–8.
- [186] Mehendale SS, Kilari Bams AS, Deshmukh CS, Dhorepatil BS, Nimbargi VN, Joshi SR. Oxidative stress-mediated essential polyunsaturated fatty acid alterations in female infertility. *Hum Fertil* 2009;12:28–33.
- [187] Merle BM, Delyfer MN, Korobelnik JF, Rougier MB, Malet F, Feart C, et al. High concentrations of plasma n3 fatty acids are associated with decreased risk for late age-related macular degeneration. *J Nutr* 2013;143:505–11.
- [188] Messa P, Londero D, Massarino F, Paganin L, Mioni G, Zattoni F, et al. Abnormal arachidonic acid content of red blood cell membranes and main lithogenic factors in

- stone formers. *Nephrol Dial Transplant Off Publ Eur Dial Transplant Assoc Eur Ren Assoc* 2000;15:1388–93.
- [189] Metcalf RG, James MJ, Mantzioris E, Cleland LG. A practical approach to increasing intakes of n-3 polyunsaturated fatty acids: use of novel foods enriched with n-3 fats. *Eur J Clin Nutr* 2003;57:1605–12.
- [190] Metherell AH, Armstrong JM, Patterson AC, Stark KD. Assessment of blood measures of n-3 polyunsaturated fatty acids with acute fish oil supplementation and washout in men and women. *Prostaglandins Leukot Essent Fat Acids* 2009;81:23–9.
- [191] Metherell AH, Buzikievich LM, Charkharzin P, Patterson AC, Peel AC, Howorth AM, et al. Omega-3 polyunsaturated fatty acid profiling using fingertip-prick whole blood does not require overnight fasting before blood collection. *Nutr Res (N Y, NY)* 2012;32:547–56.
- [192] Meydani M, Natiello F, Goldin B, Free N, Woods M, Schaefer E, et al. Effect of long-term fish oil supplementation on vitamin E status and lipid peroxidation in women. *J Nutr* 1991;121:484–91.
- [193] Moriguchi EH, Moriguchi Y, Yamori Y. Impact of diet on the cardiovascular risk profile of Japanese immigrants living in Brazil: contributions of World Health Organization CARDIAC and MONALISA studies. *Clin Exp Pharmacol Physiol* 2004;31(Suppl. 2):S5–7.
- [194] Motoyama KR, Curb JD, Kadowaki T, El-Saed A, Abbott RD, Okamura T, et al. Association of serum n-6 and n-3 polyunsaturated fatty acids with lipids in 3 populations of middle-aged men. *Am J Clin Nutr* 2009;90:49–55.
- [195] Mozaffarian D, Lemaitre RN, King IB, Song X, Huang H, Sacks FM, et al. Plasma phospholipid long-chain omega-3 fatty acids and total and cause-specific mortality in older adults: a cohort study. *Ann Intern Med* 2013;158:515–25.
- [196] Mozaffarian D, Lemaitre RN, King IB, Song X, Spiegelman D, Sacks FM, et al. Circulating long-chain omega-3 fatty acids and incidence of congestive heart failure in older adults: the cardiovascular health study: a cohort study. *Ann Intern Med* 2011;155:160–70.
- [197] Muldoon MF, Ryan CM, Sheu L, Yao JK, Conklin SM, Manuck SB. Serum phospholipid docosahexaenoic acid is associated with cognitive functioning during middle adulthood. *J Nutr* 2010;140:848–53.
- [198] Munro IA, Garg ML. Dietary supplementation with n-3 PUFA does not promote weight loss when combined with a very-low-energy diet. *Br J Nutr* 2012;108:1466–74.
- [199] Murphy KJ, Meyer BJ, Mori TA, Burke V, Mansour J, Patch CS, et al. Impact of foods enriched with n-3 long-chain polyunsaturated fatty acids on erythrocyte n-3 levels and cardiovascular risk factors. *Br J Nutr* 2007;97:749–57.
- [200] Nagasaka R, Gagnon C, Swist E, Rondeau I, Massarelli I, Cheung W, et al. EPA and DHA status of South Asian and white Canadians living in the National Capital Region of Canada. *Lipids* 2014;49:1057–69.
- [201] Nakamura T, Takebe K, Tando Y, Arai Y, Yamada N, Ishii M, et al. Serum fatty acid composition in normal Japanese and its relationship with dietary fish and vegetable oil contents and blood lipid levels. *Ann Nutr Metab* 1995;39:261–70.
- [202] Nenseter MS, Osterud B, Larsen T, Strom E, Bergei C, Hewitt S, et al. Effect of Norwegian fish powder on risk factors for coronary heart disease among hypercholesterolemic individuals. *Nutr Metab Cardiovasc Dis* 2000;10:323–30.
- [203] Newcomer LM, King IB, Wicklund KG, Stanford JL. The association of fatty acids with prostate cancer risk. *Prostate* 2001;47:262–8.
- [204] Nikkari T, Luukkainen P, Pietinen P, Puska P. Fatty acid composition of serum lipid fractions in relation to gender and quality of dietary fat. *Ann Med* 1995;27:491–8.
- [205] Njilekela M, Ikeda K, Mtabaji J, Yamori Y. Dietary habits, plasma polyunsaturated fatty acids and selected coronary disease risk factors in Tanzania. *East Afr Med J* 2005;82:572–8.
- [206] Nogi A, Yang J, Li L, Yamasaki M, Watanabe M, Hashimoto M, et al. Plasma n-3 polyunsaturated fatty acid and cardiovascular disease risk factors in Japanese, Korean and Mongolian workers. *J Occup Health* 2007;49:205–16.
- [207] Novgorodtseva TP, Denisenko YK, Zhukova NV, Antonyuk MV, Knysheva VV, Gvozdenko TA. Modification of the fatty acid composition of the erythrocyte membrane in patients with chronic respiratory diseases. *Lipids Health Dis* 2013;12:12–117.
- [208] Novgorodtseva TP, Karaman YK, Zhukova NV, Lobanova EG, Antonyuk MV, Kantor TA. Composition of fatty acids in plasma and erythrocytes and eicosanoids level in patients with metabolic syndrome. *Lipids Health Dis* 2011;10:10–82.
- [209] O'Brien DM, Kristal AR, Jeannot MA, Wilkinson MJ, Bersamin A, Luick B. Red blood cell delta15N: a novel biomarker of dietary eicosapentaenoic acid and docosahexaenoic acid intake. *Am J Clin Nutr* 2009;89:913–9.
- [210] Oda E, Hatada K, Kimura J, Aizawa Y, Thanikachalam PV, Watanabe K. Relationships between serum unsaturated fatty acids and coronary risk factors: negative relations between nervonic acid and obesity-related risk factors. *Int Heart J* 2005;46:975–85.
- [211] Ottestad I, Vogt G, Retterstol K, Myhrstad MC, Haugen JE, Nilsson A, et al. Oxidised fish oil does not influence established markers of oxidative stress in healthy human subjects: a randomised controlled trial. *Br J Nutr* 2012;108:315–26.
- [212] Palozza P, Sgarlata E, Luberto C, Piccioni E, Anti M, Marra G, et al. n-3 fatty acids induce oxidative modifications in human erythrocytes depending on dose and duration of dietary supplementation. *Am J Clin Nutr* 1996;64:297–304.
- [213] Panagiotakos DB, Mamplekou E, Pitsavos C, Kalogeropoulos N, Kistorini CM, Papageorgiou C, et al. Fatty acids intake and depressive symptomatology in a Greek sample: an epidemiological analysis. *J Am Coll Nutr* 2010;29:586–94.
- [214] Park Y, Kim M, Baek D, Kim SH. Erythrocyte n-3 polyunsaturated fatty acid and seafood intake decrease the risk of depression: case-control study in Korea. *Ann Nutr Metab* 2012;61:25–31.
- [215] Park Y, Lim J, Lee J, Kim SG. Erythrocyte fatty acid profiles can predict acute non-fatal myocardial infarction. *Br J Nutr* 2009;102:1355–61.
- [216] 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 (N Y, NY)* 2009;29:825–30.
- [217] Parkinson AJ, Cruz AL, Heyward WL, Bulkow LR, Hall D, Barstæd L, et al. Elevated concentrations of plasma omega-3 polyunsaturated fatty acids among Alaskan Eskimos. *Am J Clin Nutr* 1994;59:384–8.
- [218] Patenaude A, Rodriguez-Leyva D, Edel AL, Dibrov E, Dupasquier CM, Austria JA, et al. Bioavailability of alpha-linolenic acid from flaxseed diets as a function of the age of the subject. *Eur J Clin Nutr* 2009;63:1123–9.
- [219] Pauletto P, Puato M, Caroli MG, Casiglia E, Munhambo AE, Cazzolato G, et al. Blood pressure and atherogenic lipoprotein profiles of fish-diet and vegetarian villagers in Tanzania: the Lugalawa study. *Lancet* 1996;348:784–8.
- [220] Paunescu AC, Ayotte P, Dewailly E, Dodin S, Pedersen HS, Mulvad G, et al. Polyunsaturated fatty acids and calcaneal ultrasound parameters among Inuit women from Nuuk (Greenland): a longitudinal study. *Int J Circumpolar Health* 2013;72.
- [221] Peet M, Laugharne J, Rangarajan N, Horrobin D, Reynolds G. Depleted red cell membrane essential fatty acids in drug-treated schizophrenic patients. *J Psychiatr Res* 1995;29:227–32.
- [222] Peet M, Murphy B, Shay J, Horrobin D. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry* 1998;43:315–9.
- [223] Philibert A, Vanier C, Abdelouahab N, Chan HM, Mergler D. Fish intake and serum fatty acid profiles from freshwater fish. *Am J Clin Nutr* 2006;84:1299–307.
- [224] Phinney SD, Odin RS, Johnson SB, Holman RT. Reduced arachidonate in serum phospholipids and cholesteryl esters associated with vegetarian diets in humans. *Am J Clin Nutr* 1990;51:385–92.
- [225] 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.
- [226] Prevention. CfDca, Sciences. DoL, Health. NCFE. 2nd National report on biochemical indicators of diet and nutrition in the U.S. population; 2012 1–495.
- [227] Ratz SK, Redmon JB, Wimmergren N, Donadio JV, Bibus DM. Enhanced absorption of n-3 fatty acids from emulsified compared with encapsulated fish oil. *J Am Diet Assoc* 2009;109:1076–81.
- [228] Ratz SK, Rosenberger TA, Johnson LK, Wolters WW, Burr GS, Picklo Sr MJ. Dose-dependent consumption of farmed Atlantic salmon (*Salmo salar*) increases plasma phospholipid n-3 fatty acids differentially. *J Acad Nutr Diet* 2013;113:282–7.
- [229] Ramsden C, Gagnon C, Graciosa J, Faurot K, David R, Bralley JA, et al. Do omega-6 and trans fatty acids play a role in complex regional pain syndrome? A pilot study. *Pain Med (Malden, Mass)* 2010;11:1115–25.
- [230] Rao S, Erasmus RT. A pilot study on plasma fatty acids in poorly controlled non-insulin dependent (type 2) Melanesian diabetics. *Cent Afr J Med* 1996;42:295–7.
- [231] Reddy RD, Keshavan MS, Yao JK. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naïve baseline. *Schizophr Bull* 2004;30:901–11.
- [232] Rees D, Miles EA, Banerjee T, Wells SJ, Roynette CE, Wahle KW, et al. Dose-related effects of eicosapentaenoic acid on innate immune function in healthy humans: a comparison of young and older men. *Am J Clin Nutr* 2006;83:331–42.
- [233] Reinders I, Virtanen JK, Brouwer IA, Tuomainen TP. Association of serum n-3 polyunsaturated fatty acids with C-reactive protein in men. *Eur J Clin Nutr* 2012;66:736–41.
- [234] Rezvukhin AI, Shalaurova I, Berezovskaia EV. Effect of actual diet on fatty acid composition of blood serum and indicators of immunity in Siberian and Chukotka populations. *Vopr Med Khim* 1996;42:59–64.
- [235] Richardson AJ, Cyhlarova E, Ross MA. Omega-3 and omega-6 fatty acid concentrations in red blood cell membranes relate to schizotypal traits in healthy adults. *Prostaglandins Leukot Essent Fat Acids* 2003;69:461–6.
- [236] Rissanen H, Knekt P, Jarvinen R, Salminen I, Hakulinen T. Serum fatty acids and breast cancer incidence. *Nutr Cancer* 2003;45:168–75.
- [237] Rizzo AM, Corsetto PA, Montorfano G, Opizzi A, Faliva M, Giacosa A, et al. Comparison between the AA/EPA ratio in depressed and non depressed elderly females: omega-3 fatty acid supplementation correlates with improved symptoms but does not change immunological parameters. *Nutr J* 2012;11:82.
- [238] Rizzo AM, Montorfano G, Negroni M, Adorni L, Berselli P, Corsetto P, et al. A rapid method for determining arachidonic:eicosapentaenoic acid ratios in whole blood lipids: correlation with erythrocyte membrane ratios and validation in a large Italian population of various ages and pathologies. *Lipids Health Dis* 2010;9:7.
- [239] Rode A, Shephard RJ, Vloshinsky PE, Kuksis A. Plasma fatty acid profiles of Canadian Inuit and Siberian Ganasan. *Arctic Med Res* 1995;54:10–20.
- [240] Rodriguez Y, Giri M, Rottiers R, Christophe AB. Obese type 2 diabetics and obese patients have comparable plasma phospholipid fatty acid compositions deviating from that of healthy individuals. *Prostaglandins Leukot Essent Fat Acids* 2004;71:303–8.
- [241] Rosell MS, Lloyd-Wright Z, Appleby PN, Sanders TA, Allen NE, Key TJ. Long-chain n-3 polyunsaturated fatty acids in plasma in British meat-eating, vegetarian, and vegan men. *Am J Clin Nutr* 2005;82:327–34.
- [242] Rusca A, Di Stefano AF, Doig MV, Scarsi C, Perucca E. Relative bioavailability and pharmacokinetics of two oral formulations of docosahexaenoic acid/eicosapentaenoic acid after multiple-dose administration in healthy volunteers. *Eur J Clin Pharmacol* 2009;65:503–10.
- [243] Ruusunen A, Virtanen JK, Lehto SM, Tolmunen T, Kauhanen J, Voutilainen S. Serum polyunsaturated fatty acids are not associated with the risk of severe depression in middle-aged Finnish men: Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study. *Eur J Nutr* 2011;50:89–96.
- [244] Saadatani-Elahi M, Slimani N, Chajes V, Jenab M, Goudable J, Biessy C, et al. Plasma phospholipid fatty acid profiles and their association with food intakes: results

- from a cross-sectional study within the European Prospective Investigation into Cancer and Nutrition. *Am J Clin Nutr* 2009;89:331–46.
- [245] Sala-Vila A, Harris WS, Cofan M, Perez-Heras AM, Pinto X, Lamuela-Raventos 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.
- [246] Samieri C, Feart C, Letenneur L, Dartigues JF, Peres K, Auriaucombe S, et al. Low plasma eicosapentaenoic acid and depressive symptomatology are independent predictors of dementia risk. *Am J Clin Nutr* 2008;88:714–21.
- [247] Samieri C, Feart C, Proust-Lima C, Peuchant E, Dartigues JF, Amieva H, et al. Omega-3 fatty acids and cognitive decline: modulation by ApoEepsilon4 allele and depression. *Neurobiol Aging* 2011;32:2317 e13–22.
- [248] Samieri C, Maillard P, Crivello F, Proust-Lima C, Peuchant E, Helmer C, et al. Plasma long-chain omega-3 fatty acids and atrophy of the medial temporal lobe. *Neurology* 2012;79:642–50.
- [249] Sanders TA, Gleason K, Griffin B, Miller GJ. Influence of an algal triacylglycerol containing docosahexaenoic acid (22:6n-3) and docosapentaenoic acid (22:5n-6) on cardiovascular risk factors in healthy men and women. *Br J Nutr* 2006;95:525–31.
- [250] Schloss I, Kidd MS, Tichelaar HY, Young GO, O'Keefe SJ. Dietary factors associated with a low risk of colon cancer in coloured west coast fishermen. *S Afr Med J* 1997;87:152–8.
- [251] Sekikawa A, Curb JD, Ueshima H, El-Saed A, Kadowaki T, Abbott RD, et al. Marine-derived n-3 fatty acids and atherosclerosis in Japanese, Japanese-American, and white men: a cross-sectional study. *J Am Coll Cardiol* 2008;52:417–24.
- [252] Sekikawa A, Steingrimsdottir L, Ueshima H, Shin C, Curb JD, Evans RW, et al. Serum levels of marine-derived n-3 fatty acids in Icelanders, Japanese, Koreans, and Americans—a descriptive epidemiologic study. *Prostaglandins Leukot Essent Fat Acids* 2012;87:11–6.
- [253] Sfar S, Laporte F, Braham H, Jawed A, Amor S, Kerkeni A. Influence of dietary habits, age and gender on plasma fatty acids levels in a population of healthy Tunisian subjects. *Exp Gerontol* 2010;45:719–25.
- [254] Shannon J, King IB, Moshofsky R, Lampe JW, Gao DL, Ray RM, et al. Erythrocyte fatty acids and breast cancer risk: a case-control study in Shanghai, China. *Am J Clin Nutr* 2007;85:1090–7.
- [255] Sirov V, Dumas C, Desquilbet L, Mariotti F, Legrand P, Catheline D, et al. A restricted cubic spline approach to assess the association between high fat fish intake and red blood cell EPA + DHA content. *Nutr Metab Cardiovasc Dis* 2012;22:318–26.
- [256] Skuladottir GV, Gudmundsdottir S, Olafsson GB, Sigurdsson SB, Sigfusson N, Axelsson J. Plasma fatty acids and lipids in two separate, but genetically comparable, Icelandic populations. *Lipids* 1995;30:649–55.
- [257] Sobczak S, Honig A, Christophe A, Maes M, Helsdingen RW, De Vriese SA, et al. Lower high-density lipoprotein cholesterol and increased omega-6 polyunsaturated fatty acids in first-degree relatives of bipolar patients. *Psychol Med* 2004;34:103–12.
- [258] Solakivi T, Kaukinen K, Kunnas T, Lehtimäki T, Mäki M, Nikkari ST. Serum fatty acid profile in subjects with irritable bowel syndrome. *Scand J Gastroenterol* 2011;46:299–303.
- [259] Solomons NW, Bailey E, Soto Mendez MJ, Campos R, Kraemer K, Salem Jr N. Erythrocyte fatty acid status in a convenience sample of residents of the Guatemalan Pacific coastal plain. *Prostaglandins Leukot Essent Fat Acids* 2015;98:21–7.
- [260] Stark KD, Holub BJ. Differential eicosapentaenoic acid elevations and altered cardiovascular disease risk factor responses after supplementation with docosahexaenoic acid in postmenopausal women receiving and not receiving hormone replacement therapy. *Am J Clin Nutr* 2004;79:765–73.
- [261] Stark KD, Mulvad G, Pedersen HS, Park EJ, Dewailly E, Holub BJ. Fatty acid compositions of serum phospholipids of postmenopausal women: a comparison between Greenland Inuit and Canadians before and after supplementation with fish oil. *Nutrition*, 18. Los Angeles County, Calif: Burbank; 2002:627–30.
- [262] Stark KD, Park EJ, Maines VA, Holub BJ. Effect of a fish-oil concentrate on serum lipids in postmenopausal women receiving and not receiving hormone replacement therapy in a placebo-controlled, double-blind trial. *Am J Clin Nutr* 2000;72:389–94.
- [263] Stonehouse W, Pauga MR, Kruger R, Thomson CD, Wong M, Kruger MC. Consumption of salmon v. salmon oil capsules: effects on n-3 PUFA and selenium status. *Br J Nutr* 2011;106:1231–9.
- [264] Stough C, Downey L, Silber B, Lloyd J, Kure C, Wesnes K, et al. The effects of 90-day supplementation with the omega-3 essential fatty acid docosahexaenoic acid (DHA) on cognitive function and visual acuity in a healthy aging population. *Neurobiol Aging* 2012;33:824 e1–3.
- [265] Sublette ME, Bosetti F, DeMar JC, Ma K, Bell JM, Fagin-Jones S, et al. Plasma free polyunsaturated fatty acid levels are associated with symptom severity in acute mania. *Bipolar Disord* 2007;9:759–65.
- [266] Sublette ME, Segal-Isaacson CJ, Cooper TB, Fekri S, Vanegas N, Galfalvy HC, et al. Validation of a food frequency questionnaire to assess intake of n-3 polyunsaturated fatty acids in subjects with and without major depressive disorder. *J Am Diet Assoc* 2011;111:117–23 e1–2.
- [267] Sullivan BL, Williams PG, Meyer BJ. Biomarker validation of a long-chain omega-3 polyunsaturated fatty acid food frequency questionnaire. *Lipids* 2006;41:845–50.
- [268] Sun Q, Ma J, Campos H, Hankinson SE, Hu FB. Comparison between plasma and erythrocyte fatty acid content as biomarkers of fatty acid intake in US women. *Am J Clin Nutr* 2007;86:74–81.
- [269] Suominen-Taipale AL, Partonen T, Turunen AW, Mannisto S, Jula A, Verkasalo PK. Fish consumption and omega-3 polyunsaturated fatty acids in relation to depressive episodes: a cross-sectional analysis. *PLoS ONE* 2010;5, e10530.
- [270] Surai PF, MacPherson A, Speake BK, Sparks NH. Designer egg evaluation in a controlled trial. *Eur J Clin Nutr* 2000;54:298–305.
- [271] Surette ME, Edens M, Chilton FH, Trampusch KM. Dietary echium oil increases plasma and neutrophil long-chain (n-3) fatty acids and lowers serum triacylglycerols in hypertriglyceridemic humans. *J Nutr* 2004;134:1406–11.
- [272] Sutherland WH, Shilton ME, Nye ER, Gillies ME, Bakani I, Robertson MC. Urban/rural differences in red blood cell fatty acid composition, plasma lipids and diet in Melanesian Fijians. *Eur J Clin Nutr* 1995;49:233–41.
- [273] Takita T, Nakamura K, Kimira M, Yamada N, Kobayashi Y, Innami S. Serum fatty acid compositions and lipid concentrations and their correlations. *J Clin Biochem Nutr* 1996;20:149–59.
- [274] Thorlaksdottir AY, Skuladottir GV, Petursdottir AL, Tryggvadottir L, Ogmundsdottir HM, Eyfjord JE, et al. Positive association between plasma antioxidant capacity and n-3 PUFA in red blood cells from women. *Lipids* 2006;41:119–25.
- [275] Thorseng T, Witte DR, Vistisen D, Borch-Johnsen K, Bjerregaard P, Jørgensen ME. The association between n-3 fatty acids in erythrocyte membranes and insulin resistance: the Inuit Health in Transition Study. *Int J Circumpolar Health* 2009;68:327–36.
- [276] Tiemeier H, van Tuijl HR, Hofman A, Kiliaan AJ, Breteler MM. Plasma fatty acid composition and depression are associated in the elderly: the Rotterdam Study. *Am J Clin Nutr* 2003;78:40–6.
- [277] Toft I, Bonna KH, Ingebretsen OC, Nordoy A, Jensen T. Effects of n-3 polyunsaturated fatty acids on glucose homeostasis and blood pressure in essential hypertension. A randomized, controlled trial. *Ann Intern Med* 1995;123:911–8.
- [278] Tomiyama H, Matsumoto C, Odaira M, Yamada J, Yoshida M, Shiina K, et al. Relationships among the serum omega fatty acid levels, serum C-reactive protein levels and arterial stiffness/wave reflection in Japanese men. *Atherosclerosis* 2011;217:433–6.
- [279] Torres IC, Mira L, Ornelas CP, Melim A. Study of the effects of dietary fish intake on serum lipids and lipoproteins in two populations with different dietary habits. *Br J Nutr* 2000;83:371–9.
- [280] Tremoli E, Maderna P, Marangoni F, Colli S, Eligini S, Catalano I, et al. Prolonged inhibition of platelet aggregation after n-3 fatty acid ethyl ester ingestion by healthy volunteers. *Am J Clin Nutr* 1995;61:607–13.
- [281] Umemura U, Ishimori M, Kobayashi T, Tamura Y, Koike KA, Shimamoto T, et al. Possible effects of diets on serum lipids, fatty acids and blood pressure levels in male and female Japanese university students. *Environ Health Prev Med* 2005;10:42–7.
- [282] Vaddadi KS, Gilleard CJ, Soosai E, Polonowita AK, Gibson RA, Burrows GD. Schizophrenia, tardive dyskinesia and essential fatty acids. *Schizophr Res* 1996;20:287–94.
- [283] Valera B, Dewailly E, Anassour-Laouan-Sidi E, Poirier P. Influence of n-3 fatty acids on cardiac autonomic activity among Nunavik Inuit adults. *Int J Circumpolar Health* 2011;70:6–18.
- [284] Valsta LM, Salmelin I, Aro A, Mutanen M. Alpha-linolenic acid in rapeseed oil partly compensates for the effect of fish restriction on plasma long chain n-3 fatty acids. *Eur J Clin Nutr* 1996;50:229–35.
- [285] van den Ham EC, van Houwelingen AC, Hornstra G. Evaluation of the relation between n-3 and n-6 fatty acid status and parity in nonpregnant women from the Netherlands. *Am J Clin Nutr* 2001;73:622–7.
- [286] van der Pols JC, Xu C, Boyle GM, Hughes MC, Carr SJ, Parsons PG, et al. Serum omega-3 and omega-6 fatty acids and cutaneous p53 expression in an Australian population. *Cancer Epidemiol Biomark Prev* 2011;20:530–6.
- [287] Virtanen JK, Laukkanen JA, Mursu J, Voutilainen S, Tuomainen TP. Serum long-chain n-3 polyunsaturated fatty acids, mercury, and risk of sudden cardiac death in men: a prospective population-based study. *PLoS ONE* 2012;7, e41046.
- [288] Visioli F, Rise P, Barassi MC, Marangoni F, Galli C. Dietary intake of fish vs. formulations leads to higher plasma concentrations of n-3 fatty acids. *Lipids* 2003;38:415–8.
- [289] Vognild E, Elvevoll EO, Brox J, Olsen RL, Barstad H, Aursand M, et al. Effects of dietary marine oils and olive oil on fatty acid composition, platelet membrane fluidity, platelet responses, and serum lipids in healthy humans. *Lipids* 1998;33:427–36.
- [290] Wakai K, Ito Y, Kojima M, Tokudome S, Ozasa K, Inaba Y, et al. Intake frequency of fish and serum levels of long-chain n-3 fatty acids: a cross-sectional study within the Japan Collaborative Cohort Study. *J Epidemiol Jpn Epidemiol Assoc* 2005;15:211–8.
- [291] Wang L, Folsom AR, Eckfeldt JH. Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Nutr Metab Cardiovasc Dis* 2003;13:256–66.
- [292] Watanabe N, Watanabe Y, Kumagai M, Fujimoto K. Administration of dietary fish oil capsules in healthy middle-aged Japanese men with a high level of fish consumption. *Int J Food Sci Nutr* 2009;60(Suppl. 5):136–42.
- [293] Welch AA, Bingham SA, Iwe J, Friesen MD, Wareham NJ, Riboli E, et al. Dietary fish intake and plasma phospholipid n-3 polyunsaturated fatty acid concentrations in men and women in the European Prospective Investigation into Cancer-Norfolk United Kingdom cohort. *Am J Clin Nutr* 2006;84:1330–9.
- [294] Wennberg M, Bergdahl IA, Hallmans G, Norberg M, Lundh T, Skerfving S, et al. Fish consumption and myocardial infarction: a second prospective biomarker study from northern Sweden. *Am J Clin Nutr* 2011;93:27–36.
- [295] Whalley LJ, Fox HC, Wahle KW, Starr JM, Deary IJ. Cognitive aging, childhood intelligence, and the use of food supplements: possible involvement of n-3 fatty acids. *Am J Clin Nutr* 2004;80:1650–7.
- [296] Yamada T, Strong JP, Ishii T, Ueno T, Koyama M, Wagayama H, et al. Atherosclerosis and omega-3 fatty acids in the populations of a fishing village and a farming village in Japan. *Atherosclerosis* 2000;153:469–81.
- [297] Yaqoob P, Pala HS, Cortina-Borja M, Newsholme EA, Calder PC. Encapsulated fish oil enriched in alpha-tocopherol alters plasma phospholipid and mononuclear cell

- fatty acid compositions but not mononuclear cell functions. *Eur J Clin Invest* 2000;30:260–74.
- [298] Yeh LL, Kuller LH, Bunker CH, Ukoli FA, Huston SL, Terrell DF. The role of socioeconomic status and serum fatty acids in the relationship between intake of animal foods and cardiovascular risk factors. *Ann Epidemiol* 1996;6:290–8.
- [299] Yerlikaya FH, Mehmetoglu I, Kurban S, Tonbul Z. Plasma fatty acid composition in continuous ambulatory peritoneal dialysis patients: an increased omega-6/omega-3 ratio and deficiency of essential fatty acids. *Ren Fail* 2011;33:819–23.
- [300] Young LR, Kurzer MS, Thomas W, Redmon JB, Raatz SK. Effect of dietary fat and omega-3 fatty acids on urinary eicosanoids and sex hormone concentrations in postmenopausal women: a randomized controlled feeding trial. *Nutr Cancer* 2011;63:930–9.
- [301] Young LR, Raatz SK, Thomas W, Redmon JB, Kurzer MS. Total dietary fat and omega-3 fatty acids have modest effects on urinary sex hormones in postmenopausal women. *Nutr Metab* 2013;10:1743–7075.
- [302] Zhang J, Wang C, Li L, Man Q, Song P, Meng L, et al. Inclusion of Atlantic salmon in the Chinese diet reduces cardiovascular disease risk markers in dyslipidemic adult men. *Nutr Res (N Y, NY)* 2010;30:447–54.
- [303] Zhao M, Lamers Y, Ralat MA, Coats BS, Chi YY, Muller KE, et al. Marginal vitamin B-6 deficiency decreases plasma (n-3) and (n-6) PUFA concentrations in healthy men and women. *J Nutr* 2012;142:1791–7.
- [304] Zheng JS, Xu A, Huang T, Yu X, Li D. Low docosahexaenoic acid content in plasma phospholipids is associated with increased non-alcoholic fatty liver disease in China. *Lipids* 2012;47:549–56.
- [305] Zhou YE, Kubow S, Egeland GM. Highly unsaturated n-3 fatty acids status of Canadian Inuit: International Polar Year Inuit Health Survey, 2007–2008. *Int J Circumpolar Health* 2011;70:498–510.
- [306] Zhu J, Sun Q, Zong G, Si Y, Liu C, Qi Q, et al. Interaction between a common variant in FADS1 and erythrocyte polyunsaturated fatty acids on lipid profile in Chinese Hans. *J Lipid Res* 2013;54:1477–83.
- [307] Zhukova NV, Novgorodtseva TP. Lipid Composition of Erythrocytes at Cardiovascular and Hepatobiliary Diseases. In: Gilmore PL, editor. *Lipids: Categories, Biological Functions and Metabolism*; 2009.
- [308] Zuijgeest-van Leeuwen SD, van der Heijden MS, Rietveld T, van den Berg JW, Tilanus HW, Burgers JA, et al. Fatty acid composition of plasma lipids in patients with pancreatic, lung and oesophageal cancer in comparison with healthy subjects. *Clin Nutr (Edinburgh, Scotland)* 2002;21:225–30.
- [309] Assies J, Lievever R, Vreken P, Wanders RJ, Dingemans PM, Linszen DH. Significantly reduced docosahexaenoic and docosapentaenoic acid concentrations in erythrocyte membranes from schizophrenic patients compared with a carefully matched control group. *Biol Psychiatry* 2001;49:510–22.
- [310] Lee E, Lee S, Park Y. n-3 Polyunsaturated fatty acids and trans fatty acids in patients with the metabolic syndrome: a case-control study in Korea. *Br J Nutr* 2008;100:609–14.
- [311] Armstrong JM, Metherel AH, Stark KD. Direct microwave transesterification of fingertip prick blood samples for fatty acid determinations. *Lipids* 2008;43:187–96.
- [312] Alexander LR, Justice Jr JB, Madden J. Fatty acid composition of human erythrocyte membranes by capillary gas chromatography-mass spectrometry. *J Chromatogr* 1985;342:1–12.
- [313] Harris WS, Von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev Med* 2004;39:212–20.
- [314] Stark KD, Aristizabal Henao JJ, Metherel AH, Pilote L. Translating plasma and whole blood fatty acid compositional data into the sum of eicosapentaenoic and docosahexaenoic acid in erythrocytes. *Prostaglandins Leukot Essent Fat Acids* 2015;104:1–10.
- [315] United Nations. *Statistical Office. Population and Vital Statistics Report. Statistical Papers Series A. New York: United Nations; 2015. p. 1–23.*
- [316] Parra MS, Schnaas L, Meydani M, Perroni E, Martinez S, Romieu I. Erythrocyte cell membrane phospholipid levels compared against reported dietary intakes of polyunsaturated fatty acids in pregnant Mexican women. *Public Health Nutr* 2002;5:931–7.
- [317] Abdelmagid SA, Clarke SE, Nielsen DE, Badawi A, El-Sohemy A, Mutch DM, et al. Comprehensive profiling of plasma fatty acid concentrations in young healthy Canadian adults. *PLoS ONE* 2015;10, e0116195.
- [318] Blasbalg TL, Hibbeln JR, Ramsden CE, Majchrzak SF, Rawlings RR. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. *Am J Clin Nutr* 2011;93:950–62.
- [319] Metherel AH, Aristizabal Henao JJ, Stark KD. EPA and DHA levels in whole blood decrease more rapidly when stored at –20 degrees C as compared with room temperature, 4 and –75 degrees C. *Lipids* 2013;48:1079–91.
- [320] Metherel AH, Stark KD. Cryopreservation prevents iron-initiated highly unsaturated fatty acid loss during storage of human blood on chromatography paper at –20 degrees C. *J Nutr* 2015;145:654–60.
- [321] Stark KD. Analytical implications of routine clinical testing for omega-3 fatty acid biomarkers. *Lipid Technol* 2008;20:177–9.
- [322] Lacher DA, Hughes JP, Carroll MD. Estimate of biological variation of laboratory analytes based on the third national health and nutrition examination survey. *Clin Chem* 2005;51:450–2.
- [323] Schantz MM, Powers CD, Schleicher RL. Interlaboratory Analytical Comparison Study of Total Fatty Acid Concentrations in Human Serum: Results for Exercise 01: QA12FASER01. In: USDoC NIST, editor. *NIST Interagency/Internal Report (NISTIR) – 79532013*; 2013. p. 1–79.
- [324] von Schacky C. The Omega-3 Index as a risk factor for cardiovascular diseases. *Prostaglandins Other Lipid Mediat* 2011;96:94–8.
- [325] Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S, et al. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ* 2010;341:c6273.
- [326] Kromhout D, Giltay EJ, Geleijnse JM. Alpha Omega Trial G. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010;363:2015–26.
- [327] Brenna JT. Fatty acid analysis by high resolution gas chromatography and mass spectrometry for clinical and experimental applications. *Curr Opin Clin Nutr Metab Care* 2013;16:548–54.
- [328] Hedengran A, Szecci PB, Dyerberg J, Harris WS, Stender S. n-3 PUFA esterified to glycerol or as ethyl esters reduce non-fasting plasma triacylglycerol in subjects with hypertriglyceridemia: a randomized trial. *Lipids* 2015;50:165–75.
- [329] Browning LM, Walker CG, Mander AP, West AL, Madden J, Gambell JM, et al. 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* 2012;96:748–58.
- [330] Marangoni F, Colombo C, Galli C. A method for the direct evaluation of the fatty acid status in a drop of blood from a fingertip in humans: applicability to nutritional and epidemiological studies. *Anal Biochem* 2004;326:267–72.
- [331] Galli C, Rise P, Ghezzi S, Marangoni F. Direct determination of fatty acids in whole blood collected from fingertips: application to the assessment of fatty acid patterns (and various indexes) in population studies. *World Rev Nutr Diet* 2009;100:35–45.
- [332] Nurhasan M, Roos N, Aristizabal Henao JJ, Chamnan C, Stark KD, Lauritzen L. Effect of storage temperature in a Cambodian field setting on the fatty acid composition in whole blood. *Prostaglandins Leukot Essent Fat Acids* 2015;96:57–61.
- [333] Bjerre KS, Brubakk AM, Fougner KJ, Johnsen H, Midthjell K, Vik T. Omega-3 fatty acids: essential fatty acids with important biological effects, and serum phospholipid fatty acids as markers of dietary omega 3-fatty acid intake. *Am J Clin Nutr* 1993;57 (801S–5S; discussion 5S–6).
- [334] Lands WE. Long-term fat intake and biomarkers. *Am J Clin Nutr* 1995;61:721S–5S.
- [335] Ameur A, Enroth S, Johansson A, Zabolji G, Igl W, Johansson AC, et al. Genetic adaptation of fatty-acid metabolism: a human-specific haplotype increasing the biosynthesis of long-chain omega-3 and omega-6 fatty acids. *Am J Hum Genet* 2012;90:809–20.
- [336] Merino DM, Johnston H, Clarke S, Roke K, Nielsen D, Badawi A, et al. Polymorphisms in FADS1 and FADS2 alter desaturase activity in young Caucasian and Asian adults. *Mol Genet Metab* 2011;103:171–8.
- [337] Tanaka T, Shen J, Abecasis GR, Kisiailiou A, Ordovas JM, Guralnik JM, et al. Genome-wide association study of plasma polyunsaturated fatty acids in the InCHIANTI Study. *PLoS Genet* 2009;5, e1000338.
- [338] Crawford MA. The early development and evolution of the human brain. *Ups J Med Sci Suppl* 1990;48:43–78.
- [339] Lands WE, Morris A, Libelt B. Quantitative effects of dietary polyunsaturated fats on the composition of fatty acids in rat tissues. *Lipids* 1990;25:505–16.
- [340] Lands WE, Libelt B, Morris A, Kramer NC, Prewitt TE, Bowen P, et al. Maintenance of lower proportions of (n - 6) eicosanoid precursors in phospholipids of human plasma in response to added dietary (n - 3) fatty acids. *Biochim Biophys Acta* 1992;1180:147–62.
- [341] Lands B. A critique of paradoxes in current advice on dietary lipids. *Prog Lipid Res* 2008;47:77–106.
- [342] Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, et al. Lack of benefit of dietary advice to men with angina: results of a controlled trial. *Eur J Clin Nutr* 2003;57:193–200.
- [343] Patterson AC, Chalil A, Aristizabal Henao JJ, Streit IT, Stark KD. Omega-3 polyunsaturated fatty acid blood biomarkers increase linearly in men and women after tightly controlled intakes of 0.25, 0.5, and 1 g/d of EPA + DHA. *Nutr Res (N Y, NY)* 2015;35:1040–51.
- [344] Metherel AH, Hogg RC, Buzikievich LM, Stark KD. Butylated hydroxytoluene can protect polyunsaturated fatty acids in dried blood spots from degradation for up to 8 weeks at room temperature. *Lipids Health Dis* 2013;12:22.
- [345] Otsuka R, Kato Y, Imai T, Ando F, Shimokata H. Higher serum EPA or DHA, and lower ARA compositions with age independent fatty acid intake in Japanese aged 40 to 79. *Lipids* 2013;48:719–27.
- [346] Flock MR, Harris WS, Kris-Etherton PM. Long-chain omega-3 fatty acids: time to establish a dietary reference intake. *Nutr Rev* 2013;71:692–707.
- [347] Salem Jr N, Eggersdorfer M. Is the world supply of omega-3 fatty acids adequate for optimal human nutrition? *Curr Opin Clin Nutr Metab Care* 2015;18:147–54.
- [348] Harris WS, Mozaffarian D, Lefevre M, Toner CD, Colombo J, Cunnane SC, et al. Towards establishing dietary reference intakes for eicosapentaenoic and docosahexaenoic acids. *J Nutr* 2009;139:804S–19S.
- [349] Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA* 2006;296:1885–99.
- [350] Dyerberg J, Bang HO, Hjorne N. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am J Clin Nutr* 1975;28:958–66.
- [351] Bang HO, Dyerberg J, Nielsen AB. Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. *Lancet* 1971;1:1143–5.
- [352] Bjerregaard P, Young TK, Hegele RA. Low incidence of cardiovascular disease among the Inuit—what is the evidence? *Atherosclerosis* 2003;166:351–7.
- [353] Fodor JG, Helis E, Yazdekhesti N, Vohnout B. “Fishing” for the origins of the “Eskimos and heart disease” story: facts or wishful thinking? *Can J Cardiol* 2014;30:864–8.
- [354] Bjerregaard P. Fatal accidents in Greenland. *Arctic Med Res* 1990;49:132–41.
- [355] Bjerregaard P, Mulvad G, Pedersen HS. Cardiovascular risk factors in Inuit of Greenland. *Int J Epidemiol* 1997;26:1182–90.
- [356] Newman 3rd WP, Middaugh JP, Guzman MA, Propst MT, Rogers DR. Comparison of atherosclerosis in Alaska Natives and nonnatives. *Arch Pathol Lab Med* 1997;121:1069–75.
- [357] Pedersen HS, Mulvad G, Newman 3rd WP, Boudreau DA. Atherosclerosis in coronary arteries and aorta among Greenlanders: an autopsy study. *Atherosclerosis* 2003;170:93–103.

- [358] Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet* 1989;2:757–61.
- [359] Investigators G-P. 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* 1999;354:447–55.
- [360] Lemaitre RN, King IB, Mozaffarian D, Kuller LH, Tracy RP, Siscovick DS. n-3 Polyunsaturated fatty acids, fatal ischemic heart disease, and nonfatal myocardial infarction in older adults: the Cardiovascular Health Study. *Am J Clin Nutr* 2003;77:319–25.
- [361] Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol* 2011;58:2047–67.
- [362] Mozaffarian D, Geelen A, Brouwer IA, Geleijnse JM, Zock PL, Katan MB. Effect of fish oil on heart rate in humans: a meta-analysis of randomized controlled trials. *Circulation* 2005;112:1945–52.
- [363] Xin W, Wei W, Li XY. Short-term effects of fish-oil supplementation on heart rate variability in humans: a meta-analysis of randomized controlled trials. *Am J Clin Nutr* 2013;97:926–35.
- [364] Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. *Am J Hypertens* 2014;27:885–96.
- [365] Eslick GD, Howe PR, Smith C, Priest R, Bensoussan A. Benefits of fish oil supplementation in hyperlipidemia: a systematic review and meta-analysis. *Int J Cardiol* 2009;136:4–16.
- [366] Wei MY, Jacobson TA. Effects of eicosapentaenoic acid versus docosahexaenoic acid on serum lipids: a systematic review and meta-analysis. *Curr Atheroscler Rep* 2011;13:474–83.
- [367] Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet* 2007;369:1090–8.
- [368] Rauch B, Schiele R, Schneider S, Diller F, Victor N, Gohlke H, et al. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation* 2010;122:2152–9.
- [369] Investigators OT, Bosch J, Gerstein HC, Dagenais GR, Diaz R, Dyal L, et al. n-3 Fatty acids and cardiovascular outcomes in patients with dysglycemia. *N Engl J Med* 2012;367:309–18.
- [370] Roncaglioni MC, Tombesi M, Sillelta MG. n-3 Fatty acids in patients with cardiac risk factors. *N Engl J Med* 2013;369:781–2.
- [371] Hu FB, Manson JE. Omega-3 fatty acids and secondary prevention of cardiovascular disease—is it just a fish tale?: comment on “Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease”. *Arch Intern Med* 2012;172:694–6.
- [372] Lewis EJ. Omega-3 fatty acid supplementation and cardiovascular disease events. *JAMA* 2013;309:27.
- [373] Galli C, Brenna JT. Omega-3 fatty acid supplementation and cardiovascular disease events. *JAMA* 2013;309:28–9.
- [374] von Schacky C. Omega-3 fatty acids in cardiovascular disease—an uphill battle. *Prostaglandins Leukot Essent Fat Acids* 2015;92:41–7.
- [375] Khoueiry G, Abi Rafeh N, Sullivan E, Saiful F, Jaffery Z, Kenigsberg DN, et al. Do omega-3 polyunsaturated fatty acids reduce risk of sudden cardiac death and ventricular arrhythmias? A meta-analysis of randomized trials. *Heart Lung* 2013;42:251–6.
- [376] Joffre C, Nadjar A, Lebbadi M, Calon F, Laye S. n-3 LCPUFA improves cognition: the young, the old and the sick. *Prostaglandins Leukot Essent Fatty Acids* 2014;91:1–20.
- [377] Holman RT, Johnson SB, Hatch TF. A case of human linolenic acid deficiency involving neurological abnormalities. *Am J Clin Nutr* 1982;35:617–23.
- [378] Yurko-Mauro K, Alexander DD, Van Elswyk ME. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. *PLoS ONE* 2015;10, e0120391.
- [379] Conquer JA, Tierney MC, Zeczevic J, Bettger WJ, Fisher RH. Fatty acid analysis of blood plasma of patients with Alzheimer's disease, other types of dementia, and cognitive impairment. *Lipids* 2000;35:1305–12.
- [380] Lin PY, Chiu CC, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in dementia. *J Clin Psychiatry* 2012;73:1245–54.
- [381] de Souza Fernandes DP, Canaan Rezende FA, Pereira Rocha G, De Santis FM, Silva Moreira PR, Goncalves Alfenas Rde C. Effect of eicosapentaenoic acid and docosahexaenoic acid supplementations to control cognitive decline in dementia and Alzheimer's disease: a systematic review. *Nutr Hosp* 2015;32:528–33.
- [382] Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, et al. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch Neurol* 2006;63:1402–8.
- [383] Stonehouse W, Conlon CA, Podd J, Hill SR, Minihane AM, Haskell C, et al. DHA supplementation improved both memory and reaction time in healthy young adults: a randomized controlled trial. *Am J Clin Nutr* 2013;97:1134–43.
- [384] Eriksdotter M, Vedin I, Falahati F, Freund-Levi Y, Hjorth E, Faxen-Irving G, et al. Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's disease patients during oral omega-3 fatty acid supplementation: the OmegAD Study. *J Alzheimers Dis* 2015;48:805–12.
- [385] Verboom CN. Critical analysis of G-PT. highly purified omega-3 polyunsaturated fatty acids are effective as adjunct therapy for secondary prevention of myocardial infarction. *Herz* 2006;31(Suppl. 3):49–59.
- [386] Franzosi MG, Brunetti M, Marchioli R, Marfisi RM, Tognoni G, Valagussa F, et al. Cost-effectiveness analysis of n-3 polyunsaturated fatty acids (PUFA) after myocardial infarction: results from Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto (GISSI)-Prevenzione Trial. *Pharmacoeconomics* 2001;19:411–20.
- [387] Schmier JK, Rachman NJ, Halpern MT. The cost-effectiveness of omega-3 supplements for prevention of secondary coronary events. *Manag Care* 2006;15:43–50.
- [388] Lamotte M, Anemans L, Kawalec P, Zoellners Y. A multi-country health-economic evaluation of highly concentrated n-3 polyunsaturated fatty acids in the secondary prevention after myocardial infarction. *Herz* 2006;31(Suppl. 3):74–82.
- [389] Gissi HFI, Tavazzi L, Maggioni AP, Marchioli R, Barlera S, Franzosi MG, 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.
- [390] Cowie MR, Cure S, Bianic F, McGuire A, Goodall G, Tavazzi L. Cost-effectiveness of highly purified omega-3 polyunsaturated fatty acid ethyl esters in the treatment of chronic heart failure: results of Markov modelling in a UK setting. *Eur J Heart Fail* 2011;13:681–9.
- [391] Quilici S, Martin M, McGuire A, Zoellner Y. A cost-effectiveness analysis of n-3 PUFA (Omacor) treatment in post-MI patients. *Int J Clin Pract* 2006;60:922–32.
- [392] Samuel S, Peskin B, Arondekar B, Alperin P, Johnson S, Blumenfeld I, et al. Estimating health and economic benefits from using prescription omega-3 fatty acids in patients with severe hypertriglyceridemia. *Am J Cardiol* 2011;108:691–7.
- [393] Schmier JK, Hulme-Lowe C, Nelson JR, Chowdhury S, Everett PB, Philip S. Abstract 243: a novel cost effectiveness model of eicosapentaenoic acid (EPA) for secondary prevention in the United States. *Circ Cardiovasc Qual Outcomes* 2015;8:A243.
- [394] Hwang JY, Kim WS, Jeong S, Kwon O. Evidence-based estimation of health care cost savings from the use of omega-3 supplementation among the elderly in Korea. *Nutr Res Pract* 2015;9:400–3.
- [395] Pradelli L, Eandi M, Povero M, Mayer K, Muscaritoli M, Heller AR, et al. Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: a discrete event simulation model. *Clin Nutr (Edinburgh, Scotland)* 2014;33:785–92.
- [396] Wu GH, Gao J, Ji CY, Pradelli L, Xi QL, Zhuang QL. Cost and effectiveness of omega-3 fatty acid supplementation in Chinese ICU patients receiving parenteral nutrition. *Clinicoecon Outcomes Res* 2015;7:369–75.
- [397] Braga M, Gianotti L, Vignali A, Schmid A, Nespoli L, Di Carlo V. Hospital Resources Consumed for Surgical Morbidity: Effects of Preoperative Arginine and Omega-3 Fatty Acid Supplementation on Costs. *Nutrition*, 21. Los Angeles County, Calif: Burbank; 2005 1078–86.
- [398] Chevrou-Severac H, Pinget C, Cerantola Y, Demartines N, Wasserfallen JB, Schafer M. Cost-effectiveness analysis of immune-modulating nutritional support for gastrointestinal cancer patients. *Clin Nutr (Edinburgh, Scotland)* 2014;33:649–54.
- [399] Stark KD, Beblo S, Murthy M, Buda-Abela M, Janisse J, Rockett H, et al. Comparison of bloodstream fatty acid composition from African-American women at gestation, delivery, and postpartum. *J Lipid Res* 2005;46:516–25.
- [400] Carlson SE. Docosahexaenoic acid supplementation in pregnancy and lactation. *Am J Clin Nutr* 2009;89:678S–84S.
- [401] Ahmed S, Makrides M, Sim N, McPhee A, Quinlivan J, Gibson R, et al. Analysis of hospital cost outcome of DHA-rich fish-oil supplementation in pregnancy: evidence from a randomized controlled trial. *Prostaglandins Leukot Essent Fatty Acids* 2015;102-103:5–11.
- [402] Stark KD, Patterson AC. EPA and DHA—protein, not fat is “where it's at”? *Prostaglandins Leukot Essent Fat Acids* 2012;87:49–51.
- [403] The state of world fisheries and aquaculture/FAO Fisheries Department. 2014.
- [404] Brenna JT, Salem Jr N, Sinclair AJ, Cunnane SC. International Society for the study of fatty A, lipids I. alpha-linolenic acid supplementation and conversion to n-3 long-chain polyunsaturated fatty acids in humans. *Prostaglandins Leukot Essent Fatty Acids* 2009;80:85–91.
- [405] Eger S, Lindenmeier M, Harnack K, Krome K, Erbersdobler HF, Wahrburg U, et al. Margarines fortified with alpha-linolenic acid, eicosapentaenoic acid, or docosahexaenoic acid alter the fatty acid composition of erythrocytes but do not affect the antioxidant status of healthy adults. *J Nutr* 2012;142:1638–44.
- [406] Gibson RA, Neumann MA, Lien EL, Boyd KA, Tu WC. Docosahexaenoic acid synthesis from alpha-linolenic acid is inhibited by diets high in polyunsaturated fatty acids. *Prostaglandins Leukot Essent Fat Acids* 2013;88:139–46.
- [407] Arcand J, Scourboutakos MJ, Au JT, L'Abbe MR. Trans fatty acids in the Canadian food supply: an updated analysis. *Am J Clin Nutr* 2014;100:1116–23.
- [408] Hibbeln JR, Nieminen LR, Blasbalg TL, Riggs JA, Lands WE. Healthy intakes of n-3 and n-6 fatty acids: estimations comparing worldwide diversity. *Am J Clin Nutr* 2006;83:1483S–93S.
- [409] Kuratko C, Abril JR, Hoffman JP, Salem Jr N. 13 - Enrichment of infant formula with omega-3 fatty acids. In: Jacobsen C, Nielsen NS, Horn AF, Sorensen A-DM, editors. *Food enrichment with omega-3 fatty acids*. Woodhead Publishing; 2013. p. 353–86.
- [410] Gupta A, Barrow CJ, Puri M. Omega-3 biotechnology: thraustochytrids as a novel source of omega-3 oils. *Biotechnol Adv* 2012;30:1733–45.
- [411] Damude HG, Kinney AJ. Engineering oilseed plants for a sustainable, land-based source of long chain polyunsaturated fatty acids. *Lipids* 2007;42:179–85.
- [412] Petrie JR, Shrestha P, Zhou XR, Mansour MP, Liu Q, Belide S, et al. Metabolic engineering plant seeds with fish oil-like levels of DHA. *PLoS ONE* 2012;7, e49165.
- [413] Ji XJ, Mo KQ, Ren LJ, Li GL, Huang JZ, Huang H. Genome sequence of *Schizochytrium* sp. CCTCC M209059, an effective producer of docosahexaenoic acid-rich lipids. *Genome Announc* 2015;3.