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Review

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

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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.

Contents

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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)

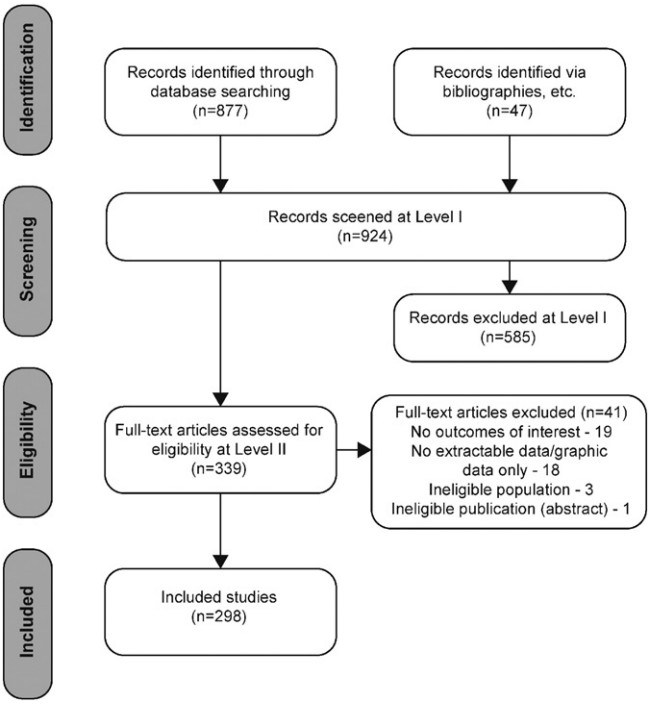

Fig. 1. Flow diagram of inclusion exclusion process.

followed by studies that had no outcomes of interest or a lack a 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 Primorsrky 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).

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.

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)

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 Primorsrky 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	20:1n−9	22:1n−9	24:1n−9	18:2n−6	18:3n−6	20:2 n−6	20:3n−6	20:4n−6	22:4n−6	22:5n−6	18:3n−3	20:5n−3	22:5n−3	22:6n−3	EPA+DHA
		Asia																									
Chien (2011)	[49]	China	986																					0.54		2.78	3.32
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				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	0.52	3.97
Sekikawa (2008)	[251]	Japan	281													26.80				6.60			0.20	2.50		5.90	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																					2.64	0.82	5.00	7.64
Yamada (2000)	[296]	Japan	261							2.70						29.90				5.90			0.63	3.80	1.34	8.40	12.20
Yamada (2000)	[296]	Japan	202							2.50						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*																*25*	*143*				*110*		*191*	*301*
Kondo (2010)[2]	[141]	*Japan*	*17*													*750*	*7*			*150*			*19*	*65*		*116*	*182*
Tomiyama (2011)[2]	[278]	*Japan*	*2206*																*33*	*172*				*52*		*122*	*174*
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		23.76		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			0.90	7.43			0.55	2.73	1.79	4.13	6.86
Manav (2004)	[178]	Singapore	145																	4.83			0.47	0.33		3.07	3.40
Manav (2004)	[178]	Singapore	147																	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	6.80
		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]	[19]	*S. Arabia*	*57*													*363*				*68*			*34*	*42*		*98*	*140*
Yerlikaya (2011)[3]	[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		1.88	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	2.83
Palozza (1996)	[212]	Italy	40													21.50			1.60	6.60	0.80			0.90	0.70	2.20	3.10
Tremoli (1995)	[280]	Italy	16													32.50				6.60				0.60		1.40	2.00
Visioli (2003)[3]	[288]	Italy	16																					0.55		1.68	2.23
Emanuele (2009)[2]	[76]	*Italy*	*60*													*387*				*71*			*33*	*37*		*84*	*120*
Torres (2000)[2]	[279]	*Portugal*	*50*		*688*	*236*										*627*			*44*	*110*			*76*	*35*		*102*	*138*
Torres (2000)[2]	[279]	*Portugal*	*37*		*717*	*247*										*666*			*53*	*145*			*60*	*20*		*61*	*82*
Amiano (2001)	[21]	Spain	102																					0.55		4.03	4.58
Carrero (2004)	[43]	Spain	30		20.05	7.32				1.00	1.34	20.66				26.41				8.25			0.32	0.56	0.81	1.83	2.39
Fernandez–Real (2003)	[78]	Spain	232	0.40	19.47	7.71	0.30	0.86	1.08			21.21			1.22	31.86	0.44			7.05			0.30	0.54		2.00	2.54
Mayneris–Perxachs (2010)	[182]	Spain	516		20.38	6.55						23.73				32.28				6.70				0.48		1.99	2.47
Rusca (2009)[2]	[242]	*Switzerland*	*48*																					*10*		*56*	*66*
Hirai (2000)[3]	[108]	NLD	39	1.51	23.29	5.06				4.17		17.75				38.62				6.93			1.04	0.27		1.31	1.58
Dangour (2010)[3]	[60]	UK	119		23.92	7.42				2.72		23.49				27.30			1.69	6.81	0.53	1.07	0.74	1.31	0.65	2.37	3.68
Leeson (2002)	[156]	UK	326																					0.70		1.86	2.56
Rosell (2005)	[241]	UK	659	1.04	21.71	6.67	0.24			1.38		22.45				33.71			1.11	5.74			1.37	0.53	0.76	1.18	1.71
Sanders (2006)[3]	[249]	UK	79		23.06	7.58				0.80		20.82				32.41			1.71	6.98	0.18	0.55	0.80	1.24	1.08	2.79	4.03
		Scandinavia																									
Reinders (2012)	[233]	Finland	1395																				0.75	1.65	0.56	2.46	4.11
Rissanen (2003)	[236]	Finland	242	1.43	25.69	8.35				3.51		24.39				24.60	0.18		1.00	2.57			0.37	0.47	0.25	0.95	1.42
Ruusunen (2011)	[243]	Finland	2031																					1.68	0.55	2.50	4.18
Solakivi (2011)	[258]	Finland	59	1.03	21.30	6.53				2.79		23.40				28.10	0.33			5.12			0.92	1.07	0.50	1.86	2.93
Suominen–Taipal (2010)	[269]	Finland	1128																	4.40				1.20	0.50	2.20	3.40
Suominen–Taipal (2010)	[269]	Finland	260																	5.95				2.04	0.65	4.15	6.19
Virtanen (2012)	[287]	Finland	1766																					1.66	0.55	2.46	4.12
Sekikawa (2012)	[252]	Iceland	97													28.00				6.32				1.66	0.72	3.04	4.70
Brox (2001)[3]	[40]	Norway	36	2.08	24.88	8.66	0.24	0.80	0.19	2.58		21.90	0.32			34.73		0.07	0.20	0.76	0.11		1.38	0.36	0.09	0.65	1.01
Grønn (1991)	[90]	Norway	15		25.00	10.00						19.40				28.00			1.60	5.60				1.70	1.50	7.30	9.00
Nenseter (2000)	[202]	Norway	70	1.00	21.30	6.70	0.10	0.30	0.20	2.10	1.60	18.80				31.40	0.30	0.20	1.10	4.80			0.50	1.90	0.50	3.80	5.70
Ottestad (2012)	[211]	Norway	54													29.90				6.20			0.60	0.60	0.50	2.10	2.70
Vognild (1998)	[289]	Norway	266	1.20	23.70	7.50				2.00	1.90	18.20	0.10			31.60	0.40		1.30	4.80			0.60	1.70	0.40	2.70	4.40
Cederholm (1994)[3]	[47]	Sweden	20	1.83	23.85	8.53	0.33		0.53	2.94		24.13			0.86	28.35		0.19	0.94	3.75			0.75	0.92		2.05	2.97
Karlsson (1996)[2]	[129]	*Sweden*	*27*													*812*	*11*		*47*	*145*			*8*	*20*	*10*	*76*	*96*

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		0.13	0.07	5.41			0.67			6.30	
Sfar (2010)	[253]	Tunisia	200		18.87	5.17						17.88				39.23				6.94			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	6.40			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	0.25	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	0.60	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*		*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*																	*352*				*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

[1]Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion
[2]Data is ug/mL
[3]Weight % data calculated from concentration data in original manuscript
[4]Weight % 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 cholesteryl 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	20:1n−9	22:1n−9	24:1n−9	18:2n−6	18:3n−6	20:2 n−6	20:3n−6	20:4n−6	22:4n−6	22:5n−6	18:3n−3	20:5n−3	22:5n−3	22:6n−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			2.20	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
Metcalf (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]	PYF	116																					1.10		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			0.70	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				0.66		10.30				22.00	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	14.20	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					2.00	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 Groote (2008)	[64]	NLD	46																					0.84		3.09	3.93
deGroot (2007)	[62]	NLD	54																	9.63	0.33	0.21		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				0.90	0.90	3.70	4.60
van den Ham (2001)	[285]	NLD	88													23.48				8.97	0.32	0.18		0.55		2.94	3.49
Zuijdgeest–Van Leeuwen (2002)	[308]	NLD	45		29.00	14.84										24.69			3.16	11.16				1.24	1.11	4.10	5.34
Kew (2004)	[133]	UK	39		27.90	11.70						9.10				21.90			3.50	13.10				1.50	0.90	7.10	8.60
Rees (2006)	[232]	UK	155													21.20	2.95			9.00				1.20	1.00	4.00	5.20
Saadatian–Elahi (2009)	[244]	UK	195	0.27	25.40	14.10	0.03			0.70	1.60	10.50	0.28			23.10	0.09	0.37	3.40	10.60	0.33	0.20	0.23	1.70	1.30	5.40	7.10
Saadatian–Elahi (2009)	[244]	UK	195	0.19	23.10	14.90	0.06			0.40	1.70	10.20	0.21			27.50	0.08	0.48	3.00	12.30	0.54	0.28	0.24	0.70	1.17	2.40	3.10
Yaqoob (2000)	[297]	UK	40																1.80	7.40				0.60		3.10	3.70
Welch (2006)[4]	[293]	*UK*	*4949*																				*0.23*	*1.27*	*1.42*	*5.21*	*6.48*
		Scandinavia																									
Madsen (2011)	[173]	Denmark	40																	9.03				2.11		5.32	7.43
Madsen (2011)	[173]	Denmark	50																	9.03				2.22		4.92	7.14
Saadatian–Elahi (2009)	[244]	Denmark	196	0.25	26.00	14.00	0.03			0.70	1.70	10.40	0.20			21.60	0.07	0.32	2.90	10.70	0.29	0.15	0.24	2.20	1.27	6.20	8.40
Laasonen (2009)[3]	[150]	Finland	36	0.60	30.16	13.07	0.30	0.83	0.59	0.73		12.57	0.30	0.06	1.55	21.26	0.06		2.52	7.40	0.10		0.35	2.18	0.82	4.57	6.75
Nikkari (1995)	[204]	Finland	84		28.33	13.24				0.93		12.31				21.18	0.07		2.74	9.25				2.03		5.84	7.87
Valsta (1996)	[284]	Finland	39	0.60	31.20	14.10				0.80	1.95	11.75				22.40			2.25	7.25				1.45	0.90	5.25	6.70
Skuladottir (1995)	[256]	Iceland	119	0.66	30.43	14.38				0.53		12.14				19.26			1.83	5.53				2.28	1.13	4.31	6.59
Almendingen (2007)	[18]	Norway	160		34.39	15.38				0.42		9.00				25.64				7.26			0.07	1.85		5.98	7.83
Bonaa (1992)	[36]	Norway	146		23.10	13.40				0.50		10.50		3.50	2.00	20.10			2.60	8.00		1.00	0.20	3.30	1.50	8.30	11.60
Brude (1997)[2]	[41]	Norway	42		26.10	15.86						10.00				23.36			3.36	9.22			0.13	1.56	1.09	6.25	7.81
Crispim (2011)	[55]	Norway	121																								7.10
Grønn (1991)	[90]	Norway	15									10.90				24.60				6.40				1.70		6.70	8.40
Grundt (1995)	[91]	Norway	57													21.30				8.50				2.60		8.05	10.65
Harvei (1997)	[103]	Norway	282	0.40	26.10	14.70	0.80	3.40	1.40	0.30		9.80	0.30		2.80	23.10		0.50	2.10	5.90			0.10	1.70	1.10	4.70	6.40
Haug (2012)	[104]	Norway	46	0.37	29.40	13.40				0.62		9.75				20.60				8.78			0.26	1.06	0.91	4.78	5.84
Hjartåker (1997)	[109]	Norway	234	0.35	25.61	13.71	0.30	0.89	0.50	0.39		9.30	0.30		1.04	24.67		0.38	2.96	8.75	0.23	0.09	0.19	1.98	1.33	6.92	8.90
Lindberg (2013)	[163]	Norway	214	0.33	24.10	13.30	0.66	2.43	0.99							20.20		0.47	3.07	8.85	0.58	0.13	0.23	2.17	1.29	7.10	9.27
Toft (1995)[5]	[277]	*Norway*	*78*																					*21*		*39*	*60*
Ambring (2006)[3]	[20]	Sweden	22		28.81	12.95	0.60	1.85	1.39	0.42		9.18			3.58	21.60	0.05	0.27	3.42	7.84			0.21	1.68		6.16	7.83
Cederholm (1994)	[47]	Sweden	20	1.10	36.10	18.60	0.48		0.89	0.70		11.10			1.40	14.70		0.30	1.85	6.50			0.13	1.07		4.47	5.54
Gustafsson (1994)	[93]	Sweden	95		0.39	14.70				0.73		12.44				21.86			3.21	8.75			0.31	1.49	1.14	4.94	6.43
Lindqvist (2009)	[164]	Sweden	254																					2.50		5.50	8.00
Wennberg (2011)	[294]	Sweden	434																					1.37		4.63	6.00
Wennberg (2011)	[294]	Sweden	122																					1.40		4.37	5.77

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		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		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		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						12.60				23.60				10.20			0.27	1.35		4.59	5.94
Metherel (2012)	[191]	Canada	8	0.55	28.44	16.14	0.40	1.10	1.06	0.46	1.69	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	0.14			18.40		0.58	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			1.92	18.96			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	0.61			13.97		0.49	1.15	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	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
Liu (2011)[4]	[166]	*USA*	*265*																					*0.50*		*1.53*	*2.03*
Raatz (2013)[4]	[228]	*USA*	*19*													*17.12*	*0.76*		*4.96*	*18.20*				*0.87*	*1.55*	*3.22*	*4.09*
Young (2013)[5]	[301]	*USA*	*17*													*286*				*123*			*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

[1]Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion
[2]Weight % data calculated from concentration data in original manuscript
[3]Weight % data calculated from mole % data in original manuscript
[4]Data is mole %
[5]Data 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
Global fatty acid compositions of erythrocytes 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	20:1n−9	22:1n−9	24:1n−9	18:2n−6	18:3n−6	20:2 n−6	20:3n−6	20:4n−6	22:4n−6	22:5n−6	18:3n−3	20:5n−3	22:5n−3	22:6n−3	EPA+DHA
		Asia																									
Huan (2004)	[115]	China	100		23.30	13.70	1.40	1.70	3.90	0.20		11.50	0.79		3.60	12.10			1.40	11.30	2.10	0.51	1.80	1.06	1.70	5.30	6.36
Junshi (1990)	[126]	China	124		24.20	14.60						13.80				8.61			1.95	14.30	1.13		0.96	0.61	1.96	4.52	5.13
Junshi (1990)	[126]	China	124		24.00	15.50						12.30				8.85			3.01	13.50	4.08		0.44	0.29	2.68	2.78	3.07
Junshi (1990)	[126]	China	124		26.60	18.00						12.30				7.83			2.49	11.90	3.59		0.44	0.22	2.01	1.86	2.08
Junshi (1990)	[126]	China	124		26.00	15.80						13.00				7.93			2.76	14.20	2.93		0.37	0.26	1.95	2.46	2.72
Junshi (1990)	[126]	China	124		25.30	17.70						13.90				7.88			2.86	10.40	4.68		0.42	0.26	1.95	2.49	2.75
Junshi (1990)	[126]	China	124		23.00	15.50						12.80				10.04			2.86	13.90	3.81		0.31	0.26	1.98	2.84	3.10
Junshi (1990)	[126]	China	124		23.20	17.60						11.70				11.69			2.89	12.40	4.89		0.40	0.42	2.62	3.00	3.42
Junshi (1990)	[126]	China	124		26.20	15.40						14.40				9.04			2.73	11.30	4.49		0.35	0.33	1.44	3.65	3.98
Junshi (1990)	[126]	China	124		25.40	15.70						14.30				8.94			2.06	12.20	1.80		0.92	0.38	1.70	2.51	2.89
Junshi (1990)	[126]	China	124		23.00	14.50						13.90				7.16			2.14	13.20	1.67		0.92	0.55	2.12	3.25	3.80
Junshi (1990)	[126]	China	124		24.10	14.90						14.40				7.80			1.98	12.50	1.63		0.94	1.30	2.37	4.53	5.83
Junshi (1990)	[126]	China	124		23.90	16.00						14.70				8.44			2.60	11.90	3.62		0.38	1.02	2.04	5.85	6.87
Junshi (1990)	[126]	China	124		25.60	16.00						15.30				7.76			2.42	12.90	2.46		0.60	0.41	2.00	2.88	3.29
Junshi (1990)	[126]	China	124		24.30	16.50						15.20				7.59			2.45	13.00	2.65		0.72	0.40	1.92	2.70	3.10
Junshi (1990)	[126]	China	124		24.10	15.60						13.30				9.77			2.14	13.60	1.75		0.76	0.28	1.66	2.45	2.73
Junshi (1990)	[126]	China	124		23.90	15.20						15.20				9.15			3.14	13.40	3.77		0.53	0.29	1.95	2.65	2.94
Junshi (1990)	[126]	China	124		24.70	15.70						14.90				7.79			2.49	12.60	2.22		0.99	0.44	2.27	2.43	2.87
Junshi (1990)	[126]	China	124		31.30	17.20						15.70				9.27			2.68	13.20	2.69		0.55	0.47	2.62	2.65	3.12
Junshi (1990)	[126]	China	124		26.60	14.40						14.50				7.93			2.23	13.00	1.46		0.96	0.51	2.23	2.59	3.10
Junshi (1990)	[126]	China	124		26.00	15.20						13.40				9.65			2.43	13.80	2.02		0.65	0.40	2.27	2.31	2.71
Junshi (1990)	[126]	China	124		24.90	16.50						14.30				7.95			2.94	12.10	4.18		0.46	0.57	1.88	3.67	4.24
Junshi (1990)	[126]	China	124		23.70	16.00						13.60				9.04			2.42	14.00	2.44		0.80	0.53	2.64	2.49	3.02
Junshi (1990)	[126]	China	124		23.50	17.00						16.60				8.11			2.87	10.80	4.06		0.70	1.20	3.07	2.12	3.32
Junshi (1990)	[126]	China	124		22.70	17.30						15.90				7.97			3.24	11.10	5.16		0.67	1.06	3.01	2.11	3.17
Liu (2003)	[167]	China	37		25.97	21.36						13.07				13.94			2.31	17.18						6.12	
Shannon (2007)	[254]	China	1030		18.73	13.93				0.20	0.93	10.50		0.35		12.17	0.08			12.08			0.27	0.60	1.86	4.92	5.52
Zhu (2013)	[306]	China	1574													14.60	0.12	0.40	1.40	13.80	3.04	1.71	0.21	0.34	1.67	3.97	4.31
Zhu (2013)	[306]	China	1636													13.60	0.11	0.38	1.27	12.00	2.24	1.33	0.29	0.57	1.80	4.85	5.42
Kale (2008)	[127]	India	46		20.08	16.54						9.68			3.53	10.86	1.40			14.68			0.19	0.17	2.98	2.79	2.96
Mehendale (2009)	[186]	India	30	0.30	20.43	15.70						10.25			3.42	11.51	0.14		1.53	14.96		3.53	0.15	0.25		2.74	2.99
Hamazaki (2006)	[95]	Japan	351													9.70				10.80				1.70		6.90	8.60
Itomura (2008)	[121]	Japan	456																					1.60		6.80	8.50
Kawabata (2011)	[130]	Japan	104													9.25			1.10	11.25			0.15	1.60	2.03	6.30	7.90
Kuriki (2006)[2]	[145]	Japan	221	0.57	27.71	21.48				1.00		17.48				10.34	0.09		0.82	10.35			0.40	1.64	1.66	6.47	8.11
Watanabe (2009)	[292]	Japan	17		21.30	14.60						14.65				10.40				13.15				3.40		11.00	14.40
Kuriki (2007)[3]	[146]	*Japan*	*357*		*31.70*															*8.70*				*1.30*	*1.10*	*4.60*	*5.90*
Gerasimova (1991)	[86]	Russia	41		21.70	11.20				3.70		13.20				11.20				3.80				1.20	2.90	4.40	5.60
Iusupova (1995)	[122]	Russia	10									15.15				10.24			.03	11.32		2.64	0.40	0.53	1.00	2.84	3.37
Gerasimova (1991)	[86]	Russia–IN	61		25.90	13.70				1.90		15.60				6.70				7.20				6.30	3.20	5.30	11.60
Novgorodtseva (2011)	[208]	Russia–PK	11	0.65	23.37	17.23	0.18			0.80	1.38	13.25				13.74		0.28	1.16	11.13	2.15	0.20		1.08	2.42	5.80	6.88
Novgorodtseva (2013)	[207]	Russia–PK	10	0.39	23.98	13.40	0.15			0.39	1.53	14.84				15.75		0.25	1.59	12.95	2.37	0.37	0.15	1.23	1.99	4.67	5.90
Zhukova (2009)	[307]	Russia–PK	1153	0.68	19.26	15.16						14.19				11.01		0.67	1.05	10.81	1.98	0.28	0.11	1.55	2.45	8.32	9.87
An (2009)	[22]	S. Korea	10	0.51	21.76	16.40			0.20	6.91		10.88	0.14		0.36	8.50	0.51	0.59	1.26	11.97		0.43	0.43	2.52	3.00	9.75	12.27
Lee (2008)	[310]	S. Korea	88	0.34	21.50	15.30				5.09		11.25				9.10	0.07			11.84			0.20	2.78	3.09	9.61	12.39
Park (2009)	[215]	S. Korea	50																								11.81
Park (2009)	[216]	S. Korea	40	0.48	22.93	17.76						13.17											0.44	1.72	2.82	8.83	10.55
Park (2012)	[214]	S. Korea	88	0.42	22.20	17.82				0.29		13.41				12.13	0.16			14.82			0.29	1.49	2.72	7.98	9.47
		Oceania																									
Brown (1991)	[39]	Australia	23		20.10	16.60	0.39	1.96			1.04				4.20	9.80			1.80	14.70	3.10			0.88	2.90	5.40	6.28
Coates (2009)	[50]	Australia	29																	12.50				0.61		2.30	2.91
James (2003)	[124]	Australia	44																					0.88	3.02	4.49	5.37
Murphy (2007)	[199]	Australia	86													6.90				11.10				0.58	2.00	3.61	4.19
Sullivan (2006)	[267]	Australia	53																					0.43	2.08	4.06	4.49
Vaddadi (1996)	[282]	Australia	39													11.46	0.13		1.48	12.06	2.56		0.14	1.03	2.44	4.62	5.65
Sutherland (1995)	[272]	Fiji	154	0.90	27.90	15.00						13.80			3.30	9.90	0.60		1.20	10.60	3.40		1.40	2.30	2.20	5.80	8.10
Stonehouse (2011)	[263]	N. Zealand	41	0.57	19.60	14.90						11.20				7.72				11.10			0.13	0.83	1.62	5.19	6.02
		Middle East																									
Freije (2009)	[82]	Bahrain	26		19.24	15.59					16.48					11.20	10.14			14.25			0.06	0.33		2.81	3.14
Green (2006)	[89]	Israel	22													11.25		0.38	1.48	14.85	3.67	0.58	0.19	0.59	2.48	5.62	6.21
Lemaitre (2008)	[158]	Israel	417		23.30	17.60			2.70			16.70				15.70			1.80	14.70	0.90			0.30		4.10	4.40
		Europe																									
Berr (2009)	[33]	France	200													9.11				13.60				1.14		6.25	7.39
Caspar–Bauguil (2010)	[44]	France	20		22.82	17.23				0.30		14.72				11.71	0.05		1.77	16.53	3.11	0.65	0.13	1.04	2.44	6.10	7.14
Caspar–Bauguil (2012)[2]	[45]	France	25		23.71	17.50				0.36		14.60				11.83			1.76	16.92	3.10		0.16	1.03	2.67	6.35	7.39
Heude (2003)	[105]	France	219		19.16	13.06						11.07				9.14				13.57				1.15		6.34	7.49
Legrand (2010)	[157]	France	160		20.10	10.50						23.10				21.50				8.90			0.42	0.67		2.60	3.27
Sirot (2012)	[255]	France	382		20.80	24.80						14.60				11.60				11.40			0.20	0.74	1.70	4.03	4.77
Baghai (2011)	[30]	Germany	80																					1.31	1.90	3.84	5.14
Dawczynski (2010)	[61]	Germany	40													6.57				14.40			0.07	0.68	1.52	2.71	3.39
Geppert (2005)	[85]	Germany	103		21.40	13.90				0.36		12.20				10.30	0.05		1.90	13.90	3.30	0.75	0.13	0.41	2.30	4.30	4.71
Kroger (2011)	[143]	Germany	2114	0.38	22.30	13.90	0.39	1.60	4.20	0.45	1.03	12.80	0.29	0.29	4.10	10.70	0.05	0.25	1.50	13.10	2.70		0.15	0.75	2.30	4.70	5.45
Imre (1994)	[118]	Hungary	5		27.50	19.40						17.20				11.20				18.90						5.70	
Cazzola (2004)[2]	[46]	Italy	100		26.56	16.30	0.53		5.49	2.61		12.71			7.52	9.95			1.03	11.40			0.23	0.63	1.52	3.51	4.14
Guarini (1998)	[92]	Italy	40	0.41	22.62	17.61	0.49	1.74	5.06			14.64	0.26			10.52		0.28		19.47			0.18	0.75		5.78	6.53
Marangoni (2007)	[180]	Italy	10		21.22	11.05						18.39				19.17			1.64	9.54			0.24	0.33	0.95	3.18	3.51
Messa (2000)	[188]	Italy	40		28.40	17.40						17.10				12.50				11.30				0.57	1.54	3.40	3.97
Paloza (1996)	[212]	Italy	40													8.68			1.65	13.58	3.43			0.70	2.28	4.98	5.68
Rizzo (2012)	[237]	Italy	76																					0.52		2.83	3.35
Leng (1999)	[161]	Scotland	770									19.58				10.20			1.04	7.59			0.25	0.68		2.37	3.05
Whalley (2004)	[295]	Scotland	60																	10.90				0.80	2.10	4.60	5.40
Duricic (2007)	[72]	Serbia	15	0.70	26.70	13.40	0.10			0.55		21.60	0.10		1.80	15.60	0.30	0.50	0.80	9.30		0.40	0.20	0.80	0.80	2.70	3.50
Sala–Vila (2011)	[245]	Spain	198	0.77	22.47	14.25	0.21	0.20		0.53		17.64	0.30		0.56	13.42	0.12		1.93	16.52			0.17	0.94	1.81	6.09	7.03
Rusca (2009)[4]	[242]	*Switzerland*	*48*																					*12*		*71*	*83*
Assies (2001)	[309]	NLD	14	0.47	25.75	17.78	0.44					12.31		0.03	3.55	11.61	0.03	0.24	1.87	14.13	2.56	0.47	0.11	0.47	1.99	3.77	4.24
De Groote (2008)[5]	[64]	NLD	46																					0.53		3.04	3.57
van den Ham (2001)	[285]	NLD	83													12.07				11.10	2.83	0.42		0.55		3.13	3.68
Leeson (2002)	[156]	UK	326																					0.47		3.06	3.53
Peet (1995)	[221]	UK	16	0.30	22.30	11.80				0.80		15.70				14.20			1.80	17.30	2.10	0.50	0.20	1.60	2.90	7.20	8.80
Peet (1998)	[22]	UK	15	0.32	19.50	18,1				0.70		15.75				10.54			1.80	14.20	3.90	1.64	0.24	0.86	2.50	5.43	6.29
Richardson (2003)	[235]	UK	25													12.17	0.03		1.42	11.69	1.72	0.21	0.12	0.86	1.83	4.28	5.14
Sanders (2006)	[249]	UK	79		19.80	16.50				0.30		14.10				11.30			1.80	16.35	3.00	0.45		1.20	2.86	6.30	7.50
		Scandinavia																									
Lauritzen (2011)	[154]	Denmark	109													10.50		0.25	1.95	15.60	3.18	0.65	0.18	0.76	2.52	5.40	6.16
Paunescu (2013)	[220]	Greenland	118													14.89	0.11	0.50	1.71	5.41	0.06	0.11	0.27	4.81	1.48	7.32	12.13
Magnusardottir (2009)	[175]	Iceland	25		19.87	15.22		1.35	3.52		1.13	12.32			3.12	9.55			1.78	13.53	2.59			0.88	2.85	6.11	6.99
Thorlaksdottir (2006)	[274]	Iceland	99		20.17	15.25		1.21	3.21			12.08			2.95	10.90			1.63	13.02	2.25			1.45	3.16	7.31	8.76
Dahl (2011)[6]	[59]	*Norway*	*53*																					*43*	*56*	*145*	*188*

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		3.58	4.22
Lucas (2009)	[169]	Canada	65													9.99				12.80			0.18	0.86	2.33	3.73	4.50
Metherel (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
Metherel (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					0.80			0.20						1.70					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																	15.75				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					2.11	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													9.53				14.04			0.19	0.61		4.17	4.78
Sun (2007)	[268]	USA	132	0.19	18.65	13.14				0.49		13.26				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

[1]Data in italics and highlighted in grey is not expressed as weight % as not enough data was published in original manuscript to allow conversion
[2]Weight % data calculated from mole % data in original manuscript
[3]Data ismole %
[4]Data is μg/mL
[5]Weight % data calculated from concentration data in original manuscript
[6]Data is μg/mg
[7]EPA+DHA was presented as weight % in original manuscript
[8]Data 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	20:1n−9	22:1n−9	24:1n−9	18:2n−6	18:3n−6	20:2 n−6	20:3n−6	20:4n−6	22:4n−6	22:5n−6	18:3n−3	20:5n−3	22:5n−3	22:6n−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																					0.61		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

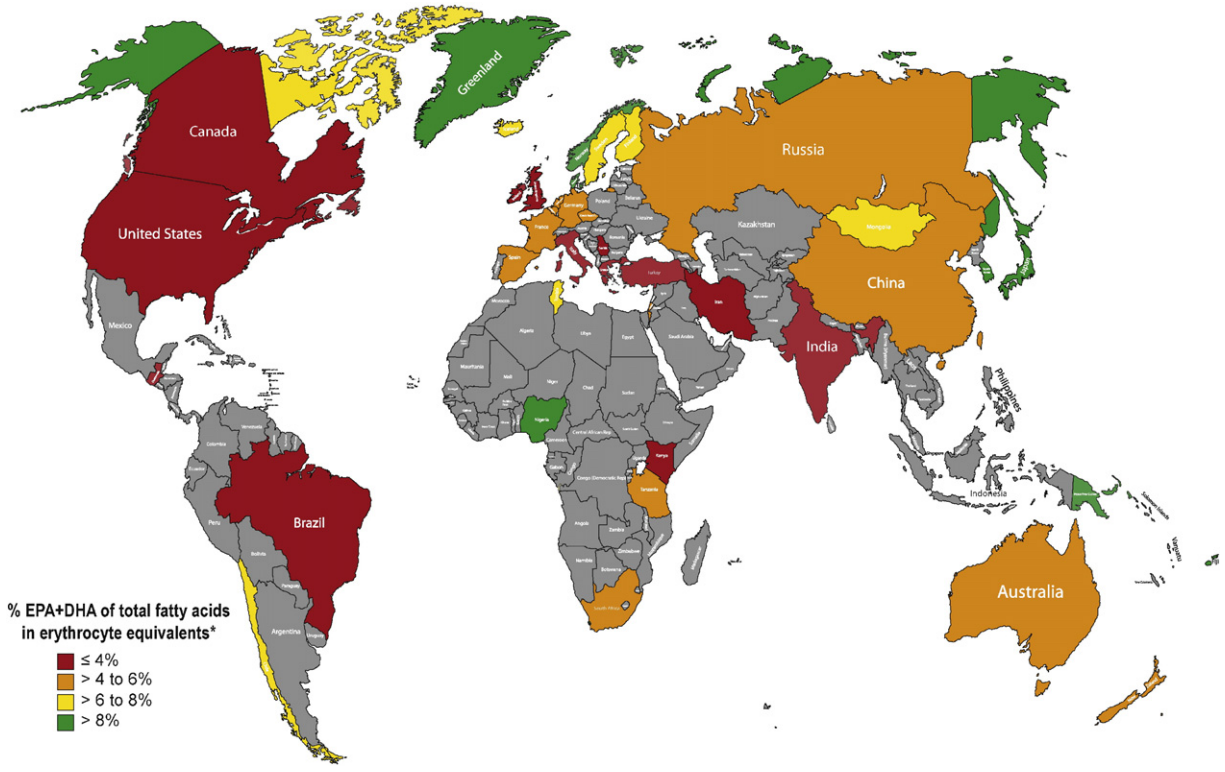

Fig. 2. Global blood levels of the sum of eicosapentaenoic acid and docosahexaenoic acid. *Fatty acid composition data from plasma total lipids, plasma phospholipids and whole blood were assigned to categorical ranges that were estimated as equivalent to erythrocyte categories [314].

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 hydroxyltoluene 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 Δ6 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 hurtles 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.

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Conflicts of interest

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