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Review Article

Omega-3 world map: 2024 update

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ABSTRACT

In 2016, the first worldwide n3 PUFA status map was published using the Omega-3 Index (O3I) as standard biomarker. The O3I is defined as the percentage of EPA + DHA in red blood cell (RBC) membrane FAs. The purpose of the present study was to update the 2016 map with new data. In order to be included, studies had to report O3I and/or blood EPA + DHA levels in metrics convertible into an estimated O3I, in samples drawn after 1999. To convert the non-RBC-based EPA + DHA metrics into RBC we used newly developed equations. Baseline data from clinical trials and observational studies were acceptable. A literature search identified 328 studies meeting inclusion criteria encompassing 342,864 subjects from 48 countries/regions. Weighted mean country O3I levels were categorized into very low ≤4%, low >4–6%, moderate >6–8%, and desirable >8%. We found that the O3I in most countries was low to very low. Notable differences between the current and 2016 map were 1) USA, Canada, Italy, Turkey, UK, Ireland and Greece (moving from the very low to low category); 2) France, Spain and New Zealand (low to moderate); and 3) Finland and Iceland (moderate to desirable). Countries such as Iran, Egypt, and India exhibited particularly poor O3I levels.

1. Introduction

Higher intakes (and thus blood levels) of omega-3 polyunsaturated fatty acids (n3 PUFAs), principally eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6), have been linked with better health outcomes across many systems.

Clinical trials and observational studies have shown that higher blood levels of EPA + DHA are associated with reductions in all-cause mortality [1–3], cardiovascular risk [3–6], risk of preterm birth [7], and regulation of normal immune response [8]. Long-chain (LC) n3 PUFA intake has also been associated with eye health [9], brain development [10], memory function in older adults [11], and mental health [12]. LC n3 PUFAs improve a variety of clinical markers such as triacylglycerol levels, blood pressure, endothelial function, and they reduce the risk of clot formation [13,14]. EPA and DHA affect membrane structure and function [15] and serve as precursors for oxygenated metabolites (oxylipins) that serve as signaling molecules [16,17].

In 2004, the Omega-3 Index (O3I) – defined as the sum of EPA + DHA in % of total fatty acids (FA) in red blood cells (RBC) – was first proposed as a risk factor for death from coronary heart disease [18]. At that time, and based on data then available, an O3I of >8% was proposed as a healthy or optimal target for reducing risk. O3I values of 4%–8% were considered "intermediate", and an O3I <4% was associated with the highest risk. In the intervening 20 years, considerable research has

Abbreviations: AT, Austria; BE, Belgium; CH, Switzerland; CZ, Czech Republic; DHA, Docosahexaenoic acid; DK, Denmark; eO3I, estimated O3I; EPA, Eicosapentaenoic acid; FA, Fatty acid; GOED, Global Organization for EPA and DHA Omega-3 s; LA, Linoleic acid; LC, Long chain; n3, omega-3; NHANES, National Health And Nutrition Examination Survey; NLD, The Netherlands; O3I, Omega-3 Index (RBC EPA + DHA%); OQA, OmegaQuant Analytics; OS, Observational study; PPC, Plasma phosphatidylcholine; PPL, Plasma phospholipid; PTL, Plasma total lipid; PUFA, Polyunsaturated fatty acid; RBC, Red blood cell; RCT, Randomized controlled trial; UK, United Kingdom; US/USA, United States of America; WB, Whole blood; w%, Weight %.

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accumulated supporting these original cut-points [1,19–22]. With "healthy" O3I levels thus defined, it became of interest to describe the O3I status, not only in research cohorts [23], but worldwide. In 2016, Stark et al. assembled the published data available from both observational and interventional studies on blood n3 levels from around the world and converted non-RBC-derived measures into an estimated O3I (eO3I) [24]. With these data in hand, these researchers created an n3 world map (Fig. 1) with four different colors depicting the estimated average O3I in every country for which data were available: red, yellow, orange and green reflecting O3I levels from <4%, 4%–6%, 6% -8%, and > 8%, respectively. There were three major messages from this original O3I map project: 1) O3I status varies widely across the world, 2) levels in most countries were less than desirable, and 3) there are many countries for which estimates of the O3I could not be made for lack of data.

The purpose of the present project was to update the original map to reflect a more current worldwide picture of n3 status. In Stark et al., inclusion criteria allowed for data from studies published as early as the 1980, and no studies published after 2014 were used to construct the map. Here, we limited ourselves to data from studies in which the blood samples were drawn between 2000 and 2023 regardless of when the report was published.

The choice of the RBC-based metric, the O3I, as the status indicator for the original map was based on the popularity of the O3I as it had been well-defined in the literature [18]. The definition of O3I was based on the RBC fraction having a longer half-life that reflects the average EPA + DHA intake of several weeks whereas the half-life of long-chain n3 PUFAs is shortest in the plasma total lipid (PTL) pool, followed by the plasma phospholipid (PPL) compartment within hours [25]. Additionally, the O3I exhibits the lowest intra-individual variability compared to PTL and PPL levels [26]. Thus, like Stark et al. in the original map, we used the O3I as the n3 biomarker of choice.

2. Review methodology

2.1. Search strategy

To identify relevant studies, a literature search was conducted between May and October 2023 using the Global Organization for EPA and DHA Omega-3 s (GOED) Clinical Study Database (CSD) [27] and PubMed (for details in search strategy see Appendix A). The search focused on identifying original research reports of observational studies (OS) and randomized controlled trials (RCTs); review articles and meta-analyses were used only to locate original publications. Demographic data such as age and gender distribution were extracted when available.

2.2. Inclusion and exclusion criteria

Inclusion criteria:

- Publication language was English.
- Only articles with full-text were included.
- Minimum age of subjects was 16 years.
- EPA and DHA levels (concentrations or relative amounts) were reported in whole blood (WB), RBCs, PTLs, PPLs, or plasma phosphatidylcholine (PPC).
- Blood samples had to be drawn in 2000 or later. For studies that did not specify a sample collection year (typically RCTs), we first attempted to contact the authors. If this was unsuccessful, we assumed that any paper published in 2004 or later used blood samples drawn in 2000 or thereafter.
- For RCTs, only baseline data were included.

Exclusion criteria:

- Studies of pregnant women and minors (<16).
- Studies that intentionally included only subjects with low or high O3I.

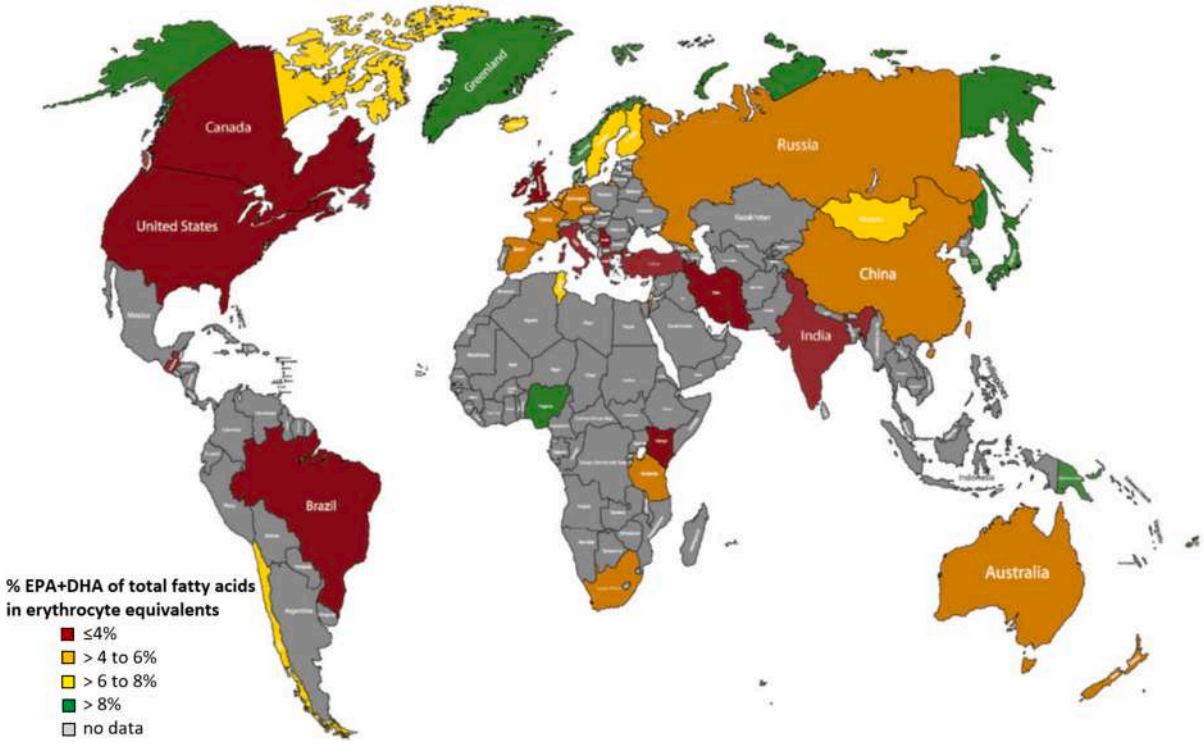


Fig. 1. 2016 global O3I map (from Stark et al. 2016, [24], an open access article under CC BY license (http://creativecommons.org/licenses/by/4.0/).

- Studies that only reported FA data from other body fluids, tissues or cells (e.g., spinal fluid, muscle, platelets, leukocytes).
- Publications where EPA and DHA levels were presented in unconvertable metrics (e.g., μg/g RBC).
- Studies whose subjects came from multiple countries.

Subjects were included regardless of health status, dietary pattern (e.g., vegans, vegetarians, Mediterranean, etc.), and fish oil supplementation status. Our goal was to describe the n3 PUFA status of populations, not to determine why they were what they were.

2.3. Initial screening and data extraction

The search results were first checked against the inclusion and exclusion criteria using titles and/or abstracts (Fig. 2). If the relevant information could not be found directly, the full texts of the publications were reviewed. Data on EPA and DHA levels, subject age, gender, study type (RCT, OS), year of baseline data collection and year of publication were extracted and transferred to the spreadsheet. We also checked to see if the EPA and DHA data came from the same study that had been published several times with a different research question (same-cohort study). In these cases, only the publication with the largest sample size was included here.

2.4. Search results

The initial searches yielded 666 references (Fig. 2). Of these, 338 were excluded due to a failure to meet all inclusion/exclusion criteria.

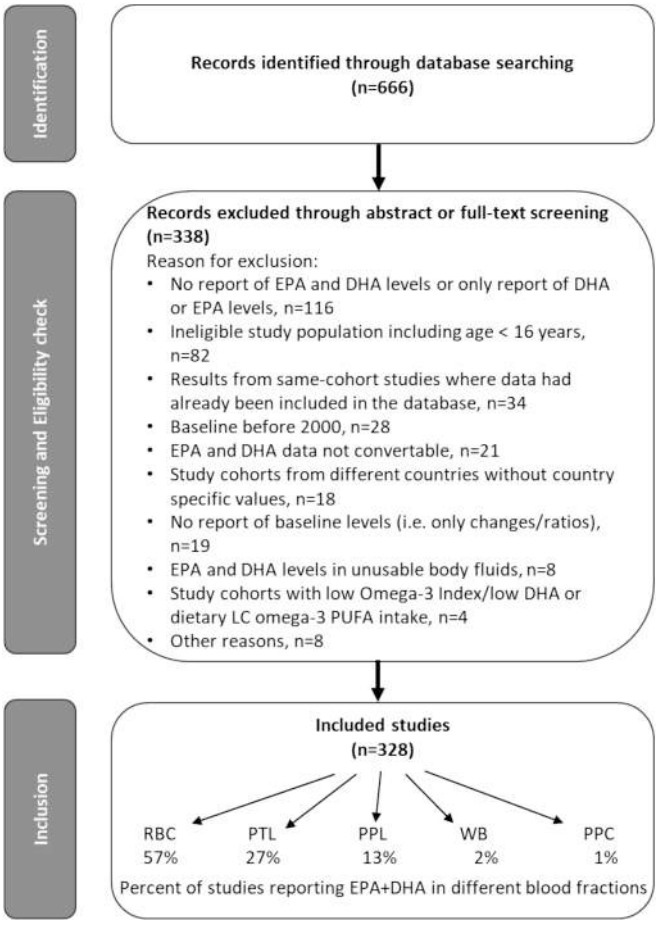


Fig. 2. Flow diagram of inclusion exclusion process.
Abbreviations: PTL, plasma total lipids; PPL, plasma phospholipids; PPC, plasma phosphatidylcholine; RBC, red blood cell; WB, whole blood.

The two most common reasons for excluding studies were that they 1) did not provide results on EPA and DHA, or 2) included ineligible populations (e.g., children, pregnant women, etc.). Although some studies had multiple reasons for being excluded, each study was only assigned to one exclusion category. In total, 328 studies were included [1,20,28–353].

2.5. Converting EPA + DHA data into the O3I

The extracted data were organized into categories based on the blood fraction analyzed: PTL, PPL, PPC, RBC, and WB. Serum was treated as plasma, and RBC-PL data were grouped under the RBC category. (This was justified by prior research indicating similarities in the FA composition of plasma and serum [354] and of RBC total lipid and RBC-PL [355].)

Studies reported EPA + DHA levels as either relative percent (expressing EPA and DHA as weight% (wt%) or Mol% of total FAs in the fraction) or absolute concentration (expressing EPA and DHA by weight or Mol per a given volume/weight of the fraction). The most prevalent expression was as a wt% (constituting 87% of the extracted data/studies), while Mol% accounted for only 4% of the data. FA levels were expressed as concentrations in 9% of the extracted data. Of this, the EPA and DHA concentrations are mainly given in μg per mL (8.3%) or using mol-based units (e.g., μmol/ml, 0.7%).

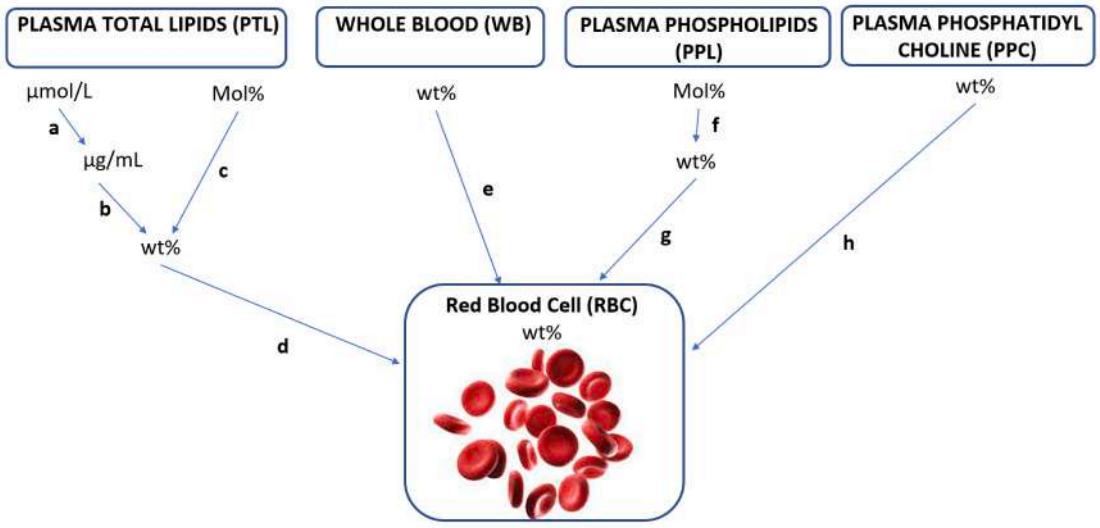
Given that EPA and DHA levels can be measured in many different pools and expressed in different ways, several equations were needed in order to convert EPA and DHA values into one, final, common status metric: the O3I (Fig. 3). Several approaches to this task were taken. Most importantly, Hu et al. expanded upon their earlier work (that used meta-analytic approaches to develop equations to convert EPA and DHA levels in PTL and PPL into RBC EPA and RBC DHA separately [356]) to convert the sum (EPA + DHA) measured in PTL and PPL into the O3I. In addition, de novo analyses were undertaken using published data from the National Health And Nutrition Examination Survey (NHANES, [357,358]) to convert plasma concentration data into percent composition. Unpublished data from OmegaQuant Analytics, LLC (OQA, Sioux Falls, SD, USA), a commercial laboratory specializing in FA testing, were used to create additional conversion equations, and equations to convert PPC into the O3I were generated by Dr. Sala-Vila using data from his laboratory in Barcelona. The details surrounding all of these conversion analyses are in Appendix A.

2.6. Calculation of the within-country O3I, categorization of the O3I, and formation of the global O3I map

For countries where several studies were available, a weighted mean (by sample size) of the O3I was calculated. For countries where only one study was available, the reported O3I value was used for the global map. Consistent with the 2016 map, the mean O3I of each country was categorized as desirable (>8%, green), moderate (>6% to 8%, yellow), low (>4% to 6%, orange), or very low (≤4%, red).

In some cases, n3 PUFA data were reported from specific regions within countries, typically those focusing on "indigenous" populations whose traditional diets differed substantially from that of the rest of the country. This applied within the USA to Alaskan Inuits; within Denmark to Greenland Inuits; and within Russia, to "indigenous" people from the Komi Republic and Nenets (Northern Russia) and from the Primorsky Krai region (Eastern Russia). These regions were colored independently of their geopolitical status.

If median values and a measure of dispersion were reported, mean values were estimated following Luo et al. (2018) [359].



	EPA+DHA: From X* to Y	Origin of data	Appendix Figure	Conversion equation	R^2
a	PTL (PPL) µmol/L (X) to PTL (PPL) µg/mL (Y)	NHANES [357, 358] n=1,974	3	y = 0.317*x + 0.8426	0.99
b	PTL µg/mL (X) to PTL wt% (Y)	NHANES [357, 358] n=1,974	4	y = 0.000246*x + 0.004451	0.77
c	PTL Mol% (X) to PTL wt% (Y)	NHANES [357, 358] n=1,974	5	y = 1.1256*x + 0.0005	0.99
d	PTL wt% (X) to RBC wt% (Y)	meta-regression analysis from 18 studies (n=979), validated with n=156 samples	1	y = 1.13*x + 2.11	0.89
e	WB wt% (X) to RBC wt% (Y)	OQA n=100 (unpublished)	6	y = 0.492*Ln(x) + 0.2199	0.89
f	PPL Mol% (X) to PPL wt% (Y)	OQA n=49 (unpublished)	7	y = 1.1169*x + 0.0016	0.99
g	PPL wt% (X) to RBC wt% (Y)	meta-regression analysis from 31 studies (n=1,701), validated with n=101 samples	2	y = 0.93*x + 0.75	0.94
h	PPC % (X) to RBC % (Y)	IMIM n=50 (unpublished)	8	y = 0.6663*x + 3.233	0.52

Fig. 3. Overview of the development of conversion equations to estimate the O3I.
Conversion equations were needed to convert EPA + DHA levels in four different pools into the eO3I. Within PTL and PPL fractions, levels expressed in concentration terms needed to be converted to percent composition terms before subsequent calculation of the eO3I. The specific equations (a-h) are given in the Table below. Note that equations a, b, c, e, f, g and h require the input of whole numbers, whereas equation e requires the input of decimal numbers only.
Abbreviations: PTL, plasma total lipids; PPL, plasma phospholipids; wt%, weight%; RBC, red blood cell; WB, whole blood; PPC, plasma phosphatidyl choline; NHANES, National Health and Nutrition Examination Survey; OQA, OmegaQuant Analytics, LLC.; IMIM, Institut Hospital del Mar d'Investigacions Mèdiques (Hospital del Mar Research Institute, Barcelona, Spain).

3. Results

3.1. Characteristics of included studies

Although the majority of studies were RCTs (79%), most subjects were from OSs (80%). (Table 1). The present study contains data on 342,864 subjects from 48 countries or regions. The average age was 53 years. The gender distribution was relatively even, with 53% women and 47% men.

It is noteworthy that nearly half of all subjects in this study came from North America (49%), mainly from the USA, followed by Europe with 43%. Hence, 92% of the data available for this n3 map were derived from about 15% of the world's countries. All other regions, including the densely populated regions of Asia, Africa, and Central and South America, account for <10% of the included studies. Countries in Central and South America, Africa, Eastern Europe, and West and Southeast Asia were severely underrepresented. In South America, data were available only from Brazil, and in Africa only from Tunisia, Egypt, Nigeria, and South Africa. Insufficient data were available to categorize Russia.

There were also clear differences in the number of individuals per region/country. Estimated O3I levels were based on <5000 individuals in all countries except Japan, China, France, the UK, Canada and the US. In 15 countries data between 1000 and 5000 individuals were available. In 30 countries there were fewer than 1000 individuals, including 14 countries with fewer than 200 individuals.

Data from formally representative population surveys were available only for Canada (Canadian Health Measures Survey, [243]) and the USA (NHANES, [292]).

EPA + DHA was reported in RBCs in 57% of studies, followed by PTL (27%) and PPL (13%); WB and PPC together accounted for 3% (Fig. 2).

Table 1
Demographics of included studies and studied subjects.

Study type	Studies n (%)[a]	Subjects n (%)
Observational studies	74 (21.4)	275,681 (80.4)
Randomized controlled trials	271 (78.6)	67,183 (19.6)
Region		
Asia	55 (16.0)	25,115 (7.3)
Oceania	31 (9.0)	2296 (0.7)
Middle East	10 (3.0)	1020 (0.3)
Europe	134 (38.5)	146,140 (42.6)
North America	99 (28.8)	166,427 (48.5)
Central and South America	6 (1.7)	760 (0.3)
Africa	10 (3.0)	1106 (0.2)

[a] Some studies include n3 PUFA data from different countries/regions. These datasets were considered as a "single study" per country/region. Therefore, the number of studies noted here (n=345) differs from the total number of studies included (n=328).

3.2. Global distribution of the O3I

The O3I data for the individual countries are shown in Table 2 and on a colored world map in Fig. 4. Detailed O3I data of the individual studies including year of baseline/study data collection, study type, demographics as well as blood fraction can be found in Appendix B.

There are major differences in EPA + DHA status around the world. While a few countries such as Iran, Egypt, the Palestinian Territories, India, Brazil or Guatemala appear to have very low O3I levels below 4% (red), most countries have an O3I in the range of 4–6% (orange). These include large parts of North America, numerous European countries, Turkey, South Africa, China and Australia. The two Russian provinces Komi Republic and Nenets in Northern Russia are also in the low O3I range. A moderate O3I (6–8%, yellow) characterized only a few countries including Spain, France, Denmark and Sweden, Tunisia, Mongolia, Taiwan and New Zealand. The eastern province of the Russian Primorsky Krai, near the Sea of Japan, and fell into this group. A desirable O3I (> 8%, green) characterized very few countries or regions, including Iceland, Norway, Finland, South Korea, and Japan, as well as Alaska (USA) and Greenland (DK).

4. Discussion

4.1. Differences between the 2024 and the 2016 maps

4.1.1. Countries included

Compared with the first n3 map by Stark et al., several countries have been added to this updated map: Mexico, Malaysia, Austria, Switzerland, Poland, Egypt, Saudi Arabia and the Palestinian Territories. However, some countries such as Chile, Tanzania, Kenya, Papua New Guinea, Central Russia, Eastern and Northern Provinces of Russia are no longer included, mainly because no data were available for blood samples collected after 1999, or the studies included very few people (e.g., only 18 in Chile and Kenya). Ultimately, 342,864 subjects from 48 countries/regions are depicted in the 2024 map, while there were 112,151 subjects from 54 countries/regions in the 2016 map.

4.1.2. Apparent changes in omega-3 status

O3I changes from the previous to the current map include 1) USA, Canada, Italy, Turkey, UK, Ireland, and Greece moving from red to orange, 2) France, Spain and New Zealand moving from orange to yellow, 3) and Finland and Iceland moving from yellow to green. In all cases where the color changed, it reflected a higher n3 status with one exception: Nigeria changed from green to orange. This was due to the substitution of a new dataset for one that was excluded [360]. Whether these represent true population changes (due to dietary changes and increased use of dietary supplements and other products containing n3 PUFA), differences in the new populations included, or to other factors differing between the two map projects are considered below.

Table 2
Global distribution of the O3I in different countries.

Region/Country	n	Age Mean/range	Male (%)	O3I (%) mean
Asia	**25,115**			
Japan	6272	61	70	9.87
South Korea	1280	50	62	9.62
Mongolia	329	46	42	6.62
China	13,296	56	47	5.55
Taiwan	1031	55	48	7.50
India	1173	28	46	3.62
Malaysia	35	65	23	4.97
Russia (Primorsky Krai)	1699	40	35	7.94
Oceania	**2296**			
Australia	2038	48	51	5.44
French Polynesia	116	46	59	6.43
New Zealand	142	42	61	6.64
Middle East	**1020**			
Iran[a]	408	30	44	2.41
Israel	211	58	88	4.72
Palestinian Territories	149	20	34	2.56
Saudi Arabia	156	52	0	4.94
Turkey	96	44	48	4.37
Europe	**146,140**			
Austria	150	40	54	4.12
Belgium	149	53	50	5.58
Czech Republic	245	53	51	4.96
Denmark	2076	55	54	7.08
Finland	1426	55	73	8.18
France	6097	70	63	6.20
Germany	3218	65	38	5.27
Greece	1014	45	50	4.53
Ireland	199	36	45	4.46
Iceland	1933	73	45	9.16
Italy	2661	58	66	5.01
Netherlands	704	65	39	4.48
Norway	4183	63	68	8.04
Poland	353	50	16	5.29
Russia (Komi Republic)	78	35	78	5.28
Russia (Nenets)	309	41	0	4.95
Serbia	274	53	45	4.64
Spain	1189	55	46	6.55
Sweden	660	63	39	6.59
Switzerland	98	44	48	5.17
United Kingdom	119,226	57	46	5.60
North America	**166,427**			
Greenland[b]	570	49	30	9.73
Canada	5919	48	50	4.83
Mexico	1497	46	5	4.33
USA	155,922	50	47	5.06
USA Alaska (Inuit)	1203	46	44	8.86
Central and South America	**760**			
Brazil	602	48	41	3.44
Guatemala	158	30	0	3.43
Africa	**1106**			
Egypt	36	31	33	2.10
Nigeria	262	39	35	5.40
South Africa	608	45	21	5.16
Tunisia	200	55	48	6.69

[a] Geopolitically assigned to the Middle East, but located in Western Asia.
[b] Autonomous territory of Denmark.

4.1.2.1. Increased omega-3 intake or decreased omega-6 intake. One possible explanation for an apparent change in a country's O3I status between the 2016 and 2024 maps could be a change in either fish consumption or n3 supplement use. It seems unlikely that global fish consumption changed significantly in recent decades, although in some countries the fish and seafood consumption has increased. In the USA for example, the National Fisheries Institute found that Americans consumed a record 9.3 kg of seafood per person in 2021, 2.7 kg more than in 2014 [361]. However, this is still below the annual fish/seafood consumption levels in countries such as Italy (23.8 to 25.2 kg/person [362]) or Germany (14.1 kg [362]), which also have average O3I levels in the orange range. On the other hand, consumer demand for n3

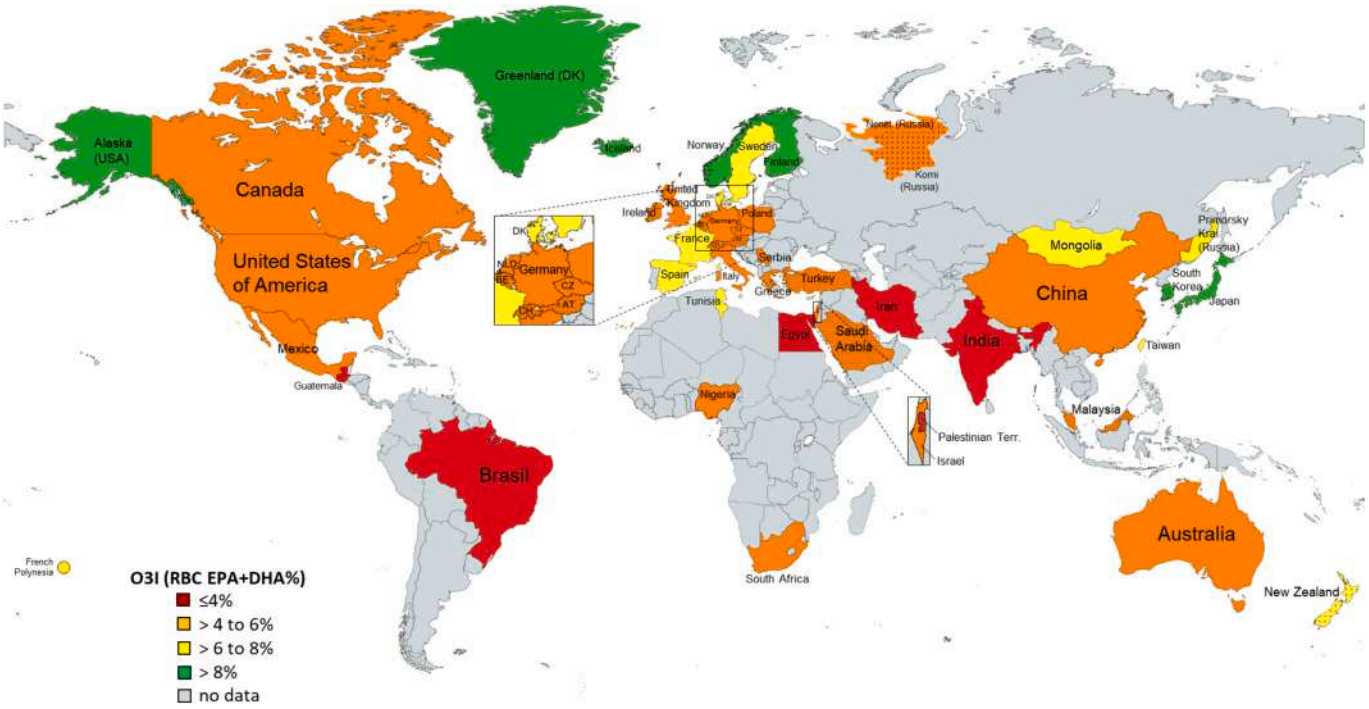


Fig. 4. 2024 global O3I map.
Global data from OSs and RCTs (baseline only) on EPA and DHA levels (concentration or relative amounts) in different blood sample types (red blood cells, plasma, plasma phospholipids, whole blood, phosphatidylcholine) were converted into an estimated O3I (eO3I). The mean O3I of each country was categorized as desirable (>8%, green), moderate (>6% to 8%, yellow), low (>4% to 6%, orange) or very low (≤4%, red). For countries where several studies were available, a weighted mean (by sample size) of O3I was calculated. Dotted countries are those with data from fewer than 200 individuals. Abbreviations: AT: Austria, BE: Belgium, CH: Switzerland, DK: Denmark, CZ: Czech Republic, NLD: The Netherlands.

supplements has increased over the last two decades. It is unclear to what extent the increase in the n3 PUFA intake is responsible for the observed shift in the O3I category in different countries.

Populations may be becoming increasingly aware of the competition between n3 and n6 PUFAs and therefore reducing their intake of linoleic acid (LA, C18:2 n6). In addition, edible oil manufacturers are now offering seed oils high in oleic acid (C18:1 n9) and low in LA, which may further reduce n6 PUFA intake [363]. However, an increase in blood EPA and DHA levels by reducing LA intake can only be expected if ALA intake is increased at the same time [152]. This is because reducing LA reduces its inhibitory effect on the conversion of ALA to EPA and DHA via desaturating and elongating enzymes [364,365].

4.1.2.2. Inclusion criteria. The general methodological approaches of the previous and current map projects were similar. Both studies searched for published data on blood EPA + DHA levels in people over 16 years of age, excluding pregnant and lactating women, and neither study pre-specified a minimum number of people per country (although, as noted above, we excluded 2 countries post hoc with data from <20 people). However, there were some differences in the inclusion criteria between the 2016 and the current (2024) map. In the former, studies published since 1980 were eligible for inclusion (but the oldest included papers were from 1990, with blood samples likely drawn in the 1980s). In the current project, we did not choose a *publication* cut-off date, but instead specified a *blood draw* cut-off date (≥ 2000). Accordingly, the "oldest data" in the current map are from 2000.

Another difference was that the first map project only included n3 data from "healthy people," that is people not known to have a given disease. (It should be noted that just because a given study did not specifically recruit patients with, for example, coronary heart disease does not necessarily mean that nobody in the study had the disease.) The reason for attempting to focus only on healthy subjects was that people with diagnosed diseases may change their dietary intake patterns. For example, there is evidence that individuals in cardiovascular clinical trials have relatively high EPA + DHA levels at baseline [184,222,366]. Alternatively, individuals with disease may have lower EPA + DHA levels. In some studies, the O3I was lower in people with metabolic disease [65,191] or urogenital disease [64] compared with healthy people, in other studies, there was no difference in the O3I between people with vs without cancer [168], CVD [100] or mental illness [106]. So, it is possible that the increases in O3I observed in some of the countries in the present map were due to the inclusion of studies that included participants motivated to consume fish or fish oil due to awareness about the potential benefits on their diagnosed disease. Finally, our goal was not to define the O3I only for "healthy" people in any given country, but for all people, healthy or not.

4.1.2.3. Different within-country datasets. The inclusion of different datasets in the 2016 map and the 2024 map is the most likely explanation for the apparent changes in the n3 status of countries. This is most clearly illustrated by the data from the USA. Classic epidemiological studies such as the Framingham Heart Study, for which O3I data were already available for 3200 people in 2012 [367], were not included in the 2016 map (mean O3I was 5.6%). The same is true for the Women's Health Initiative Memory Study [368], which included O3I data from over 8600 women from across the USA and was published in 2012 (mean O3I was 5.2%). A US clinical laboratory dataset of approximately 160,000 subjects with a mean O3I of 4.5% was published in 2013 [268], but it was not included in the 2016 map because of potential concerns about the representativeness of the clinical laboratory dataset. RBC-based data from the USA in the 2016 map included 2070 subjects from 17 studies, whereas these three excluded studies alone provided data from nearly 100 times that number, and, with O3I values between 4.5% and 5.6%, their inclusion would have changed the color of the USA in the 2016 map from red to orange.

The latest formal survey of n3 status done in the USA (NHANES) was

conducted by the Centers for Disease Control and Prevention and reported FA data collected in 2011–2012 [292]. In this survey, the mean plasma EPA + DHA level was 2.99%, which, when converted to the O3I using our equations was 5.49% and, thus, in a similar range to the average O3I value of the entire US dataset (5.06%). Estimated O3I levels were 5.21% in a very large (n = 1,169,621) clinical laboratory dataset from across the USA [369]. These data were not included in the present analysis because 1) they confirm the eO3I values that the pooled USA datasets found, and 2) the sheer size of this study would have completely swamped the USA dataset. The Canadian national survey of RBC FA levels was only published in 2015 [370] and reported an average O3I of 4.5%. These data were not available for the 2016 n3 map project (which included publications up to 2014), but if they had been available, Canada would also have been colored orange rather than red. As the Canadian National Survey is a representative sample of the entire Canadian population aged 18 and over, studies explicitly conducted among "indigenous" populations in specific regions were not included here. In the 2016 n3 map, O3I was shown independently in the northern regions of Canada and derived from studies of Canadian Inuits [371,372]. Those data were inconsistent with the Health Canada survey in that RBC PUFA levels in the Inuit cohort [371] were extremely and unexpectedly low. Why this was the case is unknown, but it could possibly have been due to storage of blood samples at −20 °C (instead of −80 °C), which is known to promote the destruction of all PUFAs, including EPA + DHA [373]. In a cross-sectional study conducted in 2004 among 861 representative Nunavik Inuit adults [374], the mean O3I ranged from 5.84% (men) to 6.86% (women), which is higher than the Canadian mean O3I.

The reasons for the higher O3I in Spain, Italy, France, Ireland and New Zealand compared to the 2016 map can be explained by the large number of OSs and RCTs conducted in the last 10 years. In the majority of these studies, the O3I tended to be higher than the average O3I in the respective countries of the 2016 n3 map. The same is true for the UK, where the average O3I in the 2016 n3 map was in the red category (<4%). Of the 22 studies evaluated here, 14 were published in the last 8 years. In all 22, the mean O3I was well above 4%. By far the largest dataset in the UK was the UK Biobank (n = 117,108) in which the mean O3I was 5.58%. This value significantly impacts the overall UK mean O3I of 5.6%. The mean O3I in the UK without the UK Biobank data would be 6.53%; almost a 1 percentage point higher. Thus, the inclusion of different datasets in the previous and new maps largely explains these three major differences.

4.1.2.4. Sample types and conversion equations. As described above, n3 PUFA levels in blood have been measured in several different blood compartments and reported in different units, ranging from wt% to molar concentrations. In the 2016 n3 map, 33% of the n3 data came from PTL, 32% from PPL, 32% from RBC and 3% from WB. A positive trend in recent years is that FA patterns in RBC are increasingly being measured in OSs and RCTs. In the current n3 map, 57% of the n3 data came from analysis of RBCs directly, while the proportion of all non-RBC based blood fractions has decreased accordingly. This means that only 43% of the non-RBC n3 values had to be converted to estimated O3I as compared to 68% in 2016.

In the original map project, conversion equations based on RBC, plasma and WB samples collected from 1104 participants and analyzed in a single lab were used to define the O3I ranges (for details see [375]). In the present project, we used equations derived from a meta-analysis of 18 or more separate studies in which plasma and RBC data were both reported. The use of the latter equations would thus be more likely to be generalizable than equations derived from a single lab. Nevertheless, in a random set of 317 plasma EPA + DHA values measured at OQA, application of the Stark equations generated virtually the same estimated O3I as did the equations by Hu et al. used in the present project (8.04% vs 8.02%). Thus, differences in conversion equations cannot explain any differences in O3I categories between the two map projects.

4.2. Countries with very low O3I, limited or no data

Alarmingly low O3I levels were observed in Iran (2.41%), Egypt (2.1%), the Palestinian Territories (2.56%), India (3.62%), Brazil (3.44%) and Guatemala (3.43%). It should be noted, however, that these numbers were calculated on the basis of very small sample sizes in each country. In Guatemala, Egypt and Palestine, the number of people was <200. In Iran, India and Brazil the number was slightly higher, but only in the parts-per-thousand-range compared to the population of these countries. Surprisingly, some western industrialized countries, such as Austria, Ireland and the Netherlands, still show O3I levels of just over 4%. Again, the O3I data in these countries were based on small sample sizes. It is unclear whether the average O3I levels measured reflect those of the population in these countries.

It is also noteworthy that the average age in countries with a very low O3I (<4%) was around 30 years (with the exception of Brazil), compared to an average age of 53 years in all countries. Previous studies have shown that the O3I tends to increase with age [268,367]. The largest dataset examining this age-related difference included 160,000 patients [268] and showed that the differences in median O3Is between individuals in their 30s and those in their 50s was 0.5 percentage points. Therefore, the young age of the cohorts in these countries does only partly explain the very low O3I.

Many countries still have virtually no population data on the O3I. This has not changed significantly since the 2016 n3 map. Most of Africa, Central and South America, South-East Asia, the Middle East and many countries in Eastern Europe do not yet have reported data on blood FA levels. Even if all countries are included in both maps, regardless of when the blood was taken, 76% of the countries of the world still has essentially no information on this important health measure.

4.3. Comparison of the n3 status with the n3 intake

It is reasonable that the observed EPA + DHA status in some countries is representative of the geographical region. This is likely to be the case for Guatemala and Brazil for Central and South America, respectively, or India for Central Asia, and Egypt, Saudi Arabia and Iran for the Middle East. This can also be deduced from the global map for n3 intake from seafood published in 2014 [376], as dietary intake of EPA + DHA is the single strongest predictor of blood levels of EPA + DHA [367,377–379]. The n3 intake map from Micha et al. showed that the intake of marine n3 PUFAs - which are mainly EPA + DHA - is quite comparable with our estimated n3 status in certain regions, although there are some exceptions. As already noted by the authors of the 2016 n3 map, there are many similarities between the global map of n3 intake from seafood and the global n3 status map. This is particularly clear in countries in the Middle East, Brazil and India, where EPA + DHA intakes and status are consistently very low. Conversely, countries with high fish consumption and high EPA + DHA intake, such as Iceland, Norway, Finland, South Korea and Japan, have desirable mean O3I values above 8%. However, Malaysia does not fit this pattern. The n3 intake map predicts a high EPA + DHA intake for Malaysia, but our (limited) data from Malaysia does not reflect this. It should be noted, however, that the data from Malaysia come from a very small sample (n = 35). Similarly, intake data from 2014 for Mexico and India are similar and very low, but n3 status in Mexico is better than in India. On the other hand, intake is reportedly quite high in the UK, Turkey and Italy, but status is not. Estimating dietary intake of EPA + DHA is difficult due to lack of detailed information on fish consumption and inadequate information on EPA + DHA levels in food databases. The extent to which national fish consumption surveys can be used to estimate national n3 status will require considerably more research.

4.4. N3 intake needed to change the O3I

Depending on the baseline O3I and the chemical formulation of EPA + DHA, prediction models can be used to calculate the dose required to raise the O3I to desirable levels [380]. For example, to move from an O3I of 4% to 8% would require an increased average intake of EPA + DHA of about 1.4 g/day [380]. Such a change in intake could be accomplished nutritionally by adding a daily serving of oily fish like salmon to the diet, or by taking n3 supplements. In addition, alternative and sustainable sources of n3 (e.g., algal sources) are becoming increasingly available [381]. The future role of genetically modified plant seeds such as Camelina [382] in providing EPA and DHA is still to be determined.

4.5. Strengths and limitations

Among the strengths of this project are the inclusion of 1) blood samples drawn in 2000 or later, 2) several major observational trial datasets, and 3) samples from all available subjects, whether deemed "healthy" or not. Compared with the 2016 map, we had less need to convert non-RBC data into RBC equivalents owing to the increased availability of original data from RBC analyses. Limitations included the lack of formal nation-wide survey data from all countries except Canada and the US, thus extrapolations had to be made from either RCT or OS data in each country, with no firm basis for assuming that these data were representative, especially from countries where the number of samples and sampling sites were very small. Searches were conducted using the GOED Clinical Study Database and PubMed; no other scientific literature databases were searched. Although the omission of other databases may have resulted in some articles being missed, there is no reason to believe that this would systematically bias our estimates. Restricting the search to English-language articles only may have missed relevant results, particularly in countries for which no other data are available. The n3 map only applies to adults and thus is not representative of levels in children or pregnant/lactating women. The consumption of fish can be influenced by various factors including education and socioeconomic status [383], the degree of urbanization [384] and proximity to fresh fish [281]. There is also data suggesting that the O3I is higher in older vs younger adults and in premenopausal women vs men [268]. As many studies do not report n3 data by age, gender and the numerous situational determinants that can influence fish consumption, it is difficult to ensure that the O3I estimates are representative of the demographics of the population in each country. It should be noted that the correlation between EPA + DHA % in PPC and RBC is low with R2 0.52, probably due to a combination of biological and analytical variability. It is uncertain whether this affects the precision of the corresponding equation. It is more likely to affect the variability than the estimated O3I. The impact on the present study should be minimal, as the PCC to eO3I equation is only used in three datasets (two in the UK, one in Brazil) with a total of <200 subjects. Given the small proportion of subjects in these datasets, it is not expected to have a significant effect on the mean O3I in these countries.

4.6. Conclusions

O3I is a widely accepted biomarker of in vivo n3 status, but more than that, it is a documented - and modifiable - risk factor for several diseases [385]. Therefore, from a public health perspective, it would be important to know the O3I status of the population so that efforts can be made to raise it to healthier levels, thereby reducing the burden of chronic disease worldwide. It has been estimated that a low seafood intake (which would be reflected in a low O3I) is the fourth most important dietary factor contributing to death from cardiovascular disease in the USA [386], and this relationship is likely to be true worldwide. Our data are consistent with this observation as the O3I was in the low to very low category in most countries around the world (where data are available). National health agencies around the world should make efforts to assess the n3 status of their populations, and based on those data, strive to improve the O3I in order to reduce risk for many of the chronic diseases plaguing the modern world.

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Authorship statement

All authors made substantial contributions to all of the following: (1) the conception and design of the study, acquisition, analysis and interpretation of data, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be submitted.

CRediT authorship contribution statement

Jan Philipp Schuchardt: Methodology, Conceptualization, Investigation, Validation, Data curation, Visualization, Writing – original draft, Supervision. **Philine Beinhorn:** Data curation, Formal analysis, Investigation, Software, Writing – original draft. **Xue Feng Hu:** Formal analysis, Writing – review & editing. **Hing Man Chan:** Formal analysis, Writing – review & editing. **Kaitlin Roke:** Methodology, Software, Writing – review & editing. **Aldo Bernasconi:** Methodology, Software, Writing – review & editing. **Andreas Hahn:** Writing – review & editing. **Aleix Sala-Vila:** Formal analysis, Writing – review & editing. **Ken D. Stark:** Writing – review & editing. **William S. Harris:** Methodology, Conceptualization, Investigation, Validation, Writing – review & editing, Resources, Funding acquisition, Supervision, Project administration.

Declaration of competing interest

WSH holds stock in OmegaQuant Analytics, LLC, a laboratory that offers FA testing. AB and KR are employees of GOED, a 501(c)6 not-for profit trade association. GOED's goals are to increase consumption of n3s to adequate levels around the world and to ensure that the industry is producing quality n3 products that consumers can trust. The other authors declare no conflicts of interest. The project was lead by WSH and JPS.

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The map was created using mapchart (https://www.mapchart.net/world.html).

Appendix A and B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plipres.2024.101286.

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