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Red Blood Cell Fatty Acid Patterns from 7 countries: Focus on the Omega-3 Index

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Declaration of Competing Interest

WSH holds stock in OmegaQuant Analytics, LLC; and CvS operates Omegametrix GmbH; laboratories that offer the O3I test. The other authors declare no conflict of interest.

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Abstract

Red blood cell (RBC) fatty acid (FA) patterns are becoming recognized as long-term biomarkers of tissue FA composition, but different analytical methods have complicated inter-study and international comparisons. Here we report RBC FA data, with a focus on the Omega-3 Index (EPA + DHA in % of total FAs in RBC), from samples of seven countries (USA, Canada, Italy, Spain, Germany, South Korea, and Japan) including 167,347 individuals (93% of all samples were from the US). FA data were generated by a uniform methodology from a variety of interventional and observational studies and from clinical laboratories. The cohorts differed in size, demographics, health status, and year of collection. Only the Canadian cohort was a formal, representative population-based survey. The mean Omega-3 Index of each country was categorized as desirable (>8%), moderate (>6% to 8%), low (>4% to 6%), or very low (≤4%). Only cohorts from Alaska (treated separately from the US), South Korea and Japan showed a desirable Omega-3 Index. The Spanish cohort had a moderate Omega-3 Index, while cohorts from the US, Canada, Italy, and Germany were all classified as low. This study is limited by the use of cohorts of convenience and small sample sizes in some countries. Countries undertaking national health status studies should utilize a uniform method to measure omega-3 FA levels.

Keywords

Omega-3 Index; fatty acid; DHA; EPA; erythrocyte; fish intake

1. Introduction

Omega-3 polyunsaturated fatty acids (n3 PUFA) may play an important role in maintaining health. In particular, the cardioprotective [1] and anti-inflammatory effects [2] of the long-chain (> C20) n3 PUFAs eicosapentaenoic acid (EPA, C20:5) and docosahexaenoic acid (DHA, C22:6) as well as their effects on brain development [3], mental health [4] and eye

health [5] have been examined in numerous randomized controlled trials and observational studies.

The Omega-3 Index (O3I) represents the sum of EPA + DHA in relation to total FA content in red blood cell (RBC) membranes. Besides its role as a coronary heart disease risk factor [6,7], the O3I is a validated biomarker of long-chain n3 PUFA intake [8] and tissue levels [9].

Numerous factors have a small impact on the O3I including age [10-12], sex [12,13], education [10,12], body mass index (BMI) [14], waist circumference [10,12], diabetes mellitus [14], smoking [10,12,15,16], and genotype [17], whereas diet, especially the intake of EPA + DHA-rich foods and supplements has the greatest impact on O3I levels [10,12,14,15]. Intake of the precursor FA alpha-linolenic acid (ALA, C18:3) only slightly contributes to the level of the O3I as **a)** the intake of ALA-rich foods (including flaxseed oil, chia seeds) is in general low, and **b)** the conversion of ALA to EPA and especially to DHA is inefficient or non-existent in humans (reviewed in [18]). A significantly better conversion to EPA + DHA was found for stearidonic acid (SDA, C18:4n3) [19], which is an n3 PUFA naturally found in very few foods (i.e., Echium oil). The consumption of fish or EPA + DHA supplements has the greatest impact on the O3I because fish contains preformed EPA and DHA (although amounts vary widely by species, season of catch, and cooking methods). Due to access and variety of dietary traditions from country to country, there are large differences in fish and seafood consumption across the world [20].

Scientific societies have made general recommendations in favour of the consumption of fish or seafood. The American Heart Association (AHA), for example, recommends 2 servings of fish (particularly fatty fish) per week [21], while in the Dietary Guidelines for Americans it is recommended to consume 225 g of a variety of seafood per week corresponding to 2-3 servings [22]. Moreover, various expert scientific organisations give specific intake recommendations for EPA + DHA. The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommends the consumption of 500 mg EPA + DHA per day for the general adult population for cardiovascular health [23].

The ISSFAL states that “the status of long chain n3 PUFAs should be measured in biological samples instead of assessing the intake of long chain n3 PUFA from the diet and/or supplements, which is not sufficient to accurately determine the long chain n3 PUFA supply in humans” [24]. The calculation of EPA + DHA intake from diet-based recall questionnaires, including nationwide nutritional surveys, is fraught with uncertainties due to over- and under-reporting of food intake, inaccurate information on EPA + DHA levels in food databases, variations due to cooking methods, and seasonal variation in n3 levels in fish to name just a few. In addition, endogenous (i.e., age, genetics) and exogenous factors (i.e., medications, smoking, other dietary factors) influencing the bioavailability or tissue incorporation of n3 PUFA are usually not taken into account [25]. An individual’s tissue EPA + DHA status can only be accurately determined by direct measurement using markers like the O3I [25-27].

If targets for healthy or desirable (or high risk) n3 PUFA status are to be established, uniform analytical methods should be employed. The n3 PUFA bio-status can be measured in several sample types, including RBC, whole plasma, whole blood, platelets, leukocytes and plasma lipid classes (i.e., phospholipids, cholesteryl esters, triglycerides, and free FAs). In 2016, a global "map" of estimated O3I levels by country was published [28] based on extrapolations from many of these sample types. The physiologically most important long chain n3 PUFAs, EPA and DHA, have different kinetics in different sample types. While long chain n3 PUFAs disappear after hours from plasma free FAs, they do so after days in plasma phospholipids, but remain in RBCs for weeks to months. This suggests that RBCs may be the preferred biomarker of long-term n3 bio-status in clinical practice and research. In addition, FAs are not equally distributed across all blood lipid fractions [29]. For example, phospholipids are enriched with PUFA, while triglycerides usually contain saturated and monounsaturated FAs (SFAs and MUFAs, respectively). Moreover, the O3I showed the lowest intra-individual variability compared to plasma and plasma phospholipid levels [30]. Different laboratory methodologies can also return different results. The original developed HS-Omega-3 Index® is defined as the EPA + DHA content of RBC as a percent of total identified FAs. This method focuses on FAs esterified in the membrane glycerophospholipids, and utilizes specific assay conditions (e.g., reagents, solvents, temperatures, times, etc.). Other methodologies focus on FAs esterified in glycerophospholipids and sphingolipids, and consistently show significantly higher levels of the sphingolipid FAs and, thus, lower levels of the n3 PUFAs [27]. This discrepancy underscores the need for a uniform, ideally standardized methodology for measuring the O3I.

The aim of our *7-countries omega-3 study* was to assess the average n3 bio-status across countries by categorizing the O3I levels as desirable (>8%), moderate (>6 to 8%), low (>4 to 6%), or very low (≤4%) similar to the categories used in the first global n3 status study conducted by Stark et al. [28]. Although originally only three categories for the classification of the O3I were proposed (desirable ≥8%, suboptimal <8 to 4%, low ≤4%) [6], the 4-group categorisation was applied here to enable a re-examination of Stark et al.. A secondary aim of our study was to provide data on the full RBC FA profile from these countries, as such data are not currently in the literature. To accomplish these aims, we examined data from 18 cohorts where the RBC FA profile including the O3I was directly measured using the HS-Omega-3 Index® methodology.

2. Methods

2.1. Included Studies

The RBC FA data reported here derive from both published and unpublished studies, including randomized controlled trials (RCTs), observational studies, a national survey, and clinical laboratories. Only baseline data were used from RCTs. The only selection criterion for these studies was that RBC FA data were generated using the HS-Omega-3 technology. This removed potential inconsistencies arising from differences in laboratory methods.

Overall, RBC FA data from 167,347 individuals from 18 cohorts and 7 countries were evaluated. Most RBC FA data were collected in the United States with 156,293 study

samples (Table 1) which, together, made up 93% of all analysis. Eighty-eight % of the US data came from clinical laboratories (Table 2).

Because specific information on sex or age were not available on an individual basis (particularly from the clinical lab datasets), relationships between these variables and RBC FA data could not be explored. Similarly, we did not present measures of variance and percentile distributions because the necessary data were not consistently available.

Only the Canadian Health Measures Survey (CHMS, n = 4,025) was a representative, nation-wide, population screening project. All other study cohorts differed in background (i.e., geography, demographics, and clinical condition) and sampling period.

2.2. Laboratory Methods

The laboratories involved include those of Dr. Yongsoon Park (Seoul, Korea), Dr. Clemens von Schacky (Martinsried, Germany) and Dr. William Harris (Sioux Falls, South Dakota, USA). Data from Dr. Aleix Sala-Vila's lab in Barcelona (Spain) were also included, because the method used there had been previously validated against the reference method [16].

Briefly, blood was drawn into an EDTA tube, and RBC were separated from plasma by centrifugation. Unless analysed immediately, the RBC fraction was frozen at −80°C after collection. RBC were incubated at 100°C with boron trifluoride–methanol and hexane for 10 minutes to generate FA methyl esters that were then extracted by the addition of water and subsequently analysed by GC with flame ionization detection. Twenty-one FAs were quantified and expressed as a percentage of total RBC FAs, and the O3I was computed as the sum of EPA + DHA. The 18-carbon trans FAs were summed by degree of unsaturation into total 18:1 or total 18:2 trans species. The analytical variability of EPA + DHA using the HS-Omega-3 Index® method is 4.1%±1.9% [30].

2.3. Statistical Analysis

Mean values for all RBC FAs were calculated in each dataset. When summarizing whole-country data with several data sets (i.e., USA, Germany), a weighted average was calculated, considering the size of the individual data sets. The mean O3I of a country-specific dataset was categorized as desirable (>8%), moderate (>6 to 8%), low (>4 to 6%), or very low (≤4%).

3. Results

3.1 Characterization of cohorts

Most cohorts had a relatively even male/female distribution whereas a few cohorts had only one sex (Table 1 and 2). The mean age of study participants in the different cohorts (excluding Canada-CHMS) generally ranged between 40 and 68 y. Participants were mostly healthy, except for cohorts including participants free of known CVD but at increased risk for CVD (Spain-PREDIMED and Germany-LURIC), or with diagnosed CVD (Italy-GISSI-HF and Germany-LURIC). With a few exceptions (Germany-LURIC 1997-2000, US-WHI-MS 1993), most of the samples were taken within the last 20 y.

3.2 Omega-3 Index

The mean O3I was in the desirable range in cohorts from Alaska (9.10%), South Korea (9.26%) and Japan (9.58%; Table 1 and 2). With a mean O3I of 7.05%, the Spanish (Barcelona) cohort was in the moderate range, whereas all other cohorts/countries exhibited low mean O3I values: Canada (4.50%), all US-cohorts excluding Alaska (weighted average mean: 5.44%), two German cohorts (weighted average mean: 5.80%), and the Italian cohort (4.75%). No cohort showed a very low mean O3I.

3.3 Other FAs

RBC linoleic acid (LA, C18:2n6) levels were largely constant in the range between 11 and 13% of total FA among the cohorts from different countries. This also applied to the two Asian cohorts from South Korea (LA: 12.7%) and Japan (LA: 12.0%). It should be noted that mean EPA, DHA and O3I levels were in a similar range in these two cohorts.

Arachidonic acid (ARA, C20: 4n6) levels were in a relatively constant range, between 14 and 17%, in all cohorts with low O3I, while in the cohorts from Alaska, South Korea and Japan it was significantly lower, at ~ 12% of total FA in RBC.

Although ALA levels were < 0.4% of total FA in RBC, there were relatively large inter-cohort differences. For example, the highest ALA level (0.39%) was found in South Korea followed by Canada and Japan at 0.29% and 0.26%, respectively. Average ALA levels of the other cohorts / countries were lower (0.10% and 0.20%).

Oleic acid (C18:1n9) levels in the Italian (18.9%) and Spanish cohorts (17.6%) were higher compared to other cohorts, in which the levels ranged between 13.5 and 16.5%.

Differences in trans FA levels between cohorts were also considerable. Some cohorts had low total trans FA levels (0.66% in Italy; 0.65% in Japan; 0.59% in Canada), while several US-cohorts had three to four times higher trans FA levels in RBC (2.70% in WHI-MS; 2.10% in Alaska and Framingham Offspring).

4. Discussion

The first n3 bio-status world map was “painted” by Stark and co-authors almost 6 y ago, comparing the estimated O3I calculated from relative EPA + DHA weight percentages (wt.%) from various blood fractions (i.e., plasma total lipids, plasma phospholipids, and whole blood), as reported in different studies. In the Stark map, very low n3 levels (<4% EPA + DHA of total FAs in RBC equivalents) were reported for the US, Canada, United Kingdom, Ireland, Italy, Turkey and India. In addition, the n3 bio-status in countries such as Spain, France, Germany, Holland, Belgium, the Czech Republic, South Africa and Australia was considered low (>4-6% EPA + DHA of total FAs in RBC equivalents).

Our study was based on directly analysed O3I values and showed better n3 bio-status for several of the countries in the Stark study. Specifically, the US (excluding Alaska), Canada, and Italy, which Stark reported as “very low” actually were in the “low” category. Spain also showed better status than assumed by Stark, with a "moderate" category, rather than

"low". On the other hand, our data for Germany concur with Stark's "low" categorization. For South Korea, Japan, and Alaska, our finding that average O3I levels were >8% agree with Stark's map. Consistent with the literature, these three cohorts also had the lowest mean ARA levels.

The intake of EPA + DHA-rich fish is the most important driver of O3I besides EPA + DHA supplements. The desirable O3I values in Japan, South Korea, and Alaska are plausible, as fish (and/or seal and whale) consumption in these countries is high. For example, fish consumption in South Korea (55.0 kg/capita/y, [31]) and Japan (45.5 kg/capita/y, [31]) are the highest in the world. The GOCADAN Cohort in Alaska consisted predominantly of "Western Alaskan Native (Inupiat)", who have shown lifestyle changes toward the western diet, but who still have relatively high fish consumption, at least during the period of the study (2000-2004). The authors of the GOCADAN study reported that the total n3 PUFA intake was between 3.0 and 4.3 g/d, depending on age, with seal oil and salmon as the major sources of n3 PUFAs for all age-sex groups [32]. Hence, the majority of the n3 PUFA were ingested as preformed EPA + DHA. In contrast, according to NHANES data, the average EPA + DHA intake in the US in 2003-2014 was considerably lower, at 100 mg/d [33].

The cohort in Spain/Barcelona – although small in size – appears to be representative for the Spanish population in view of reported fish consumption for Spain. In this particular cohort fish intake – calculated via Food Frequency Questionnaires – was 116 g/d, which corresponds to 42.3 kg/y. This exactly conforms with the average amount of fish and shellfish consumed in Spain (42.4 kg/capita/y) according to statistics from the United Nations Food and Agriculture Organization (FAO) [31]. The mean O3I of 7.05% was also in a range suggesting high fish consumption. The reason why the O3I is not even higher (in Japan the O3I is 9.58% with slightly higher fish consumption) could be a relatively lower proportion of high-fat fish. Accordingly, the proportion of high-fat fish is only 22% of total fish consumption (corresponding to 25 g/d) in the PREDIMED cohort. Nevertheless, the calculated mean EPA + DHA intake was still 0.9 g/d.

The Italian cohort had a relatively low O3I (4.75%). Actual fish consumption in Italy is not clear, however. The annual per capita fish intake in Italy between 2002 to 2005 was estimated by FAO as 23.8 to 25.2 kg [31]. In the European Investigation into Cancer and Nutrition (EPIC) study, total fish intake in Italy was 7 to 13 kg/y per capita, depending on the region [34]. The low mean O3I in Italy might be explained by the choice of fish. In general, low-fat fish and seafood – which is also low in EPA and DHA – are consumed in Mediterranean countries such as Italy or Greece. According to the EPIC study, intake of fatty fish was, indeed, low in Italy estimated at 3 to 6 kg/y, corresponding to 8 to 16 g/d [34]. No data from Greece were available in our study. In the report by Stark et al., Greece showed a very low O3I value. This partly explains the discrepancy between Italy and Germany, where the weighted average mean of the O3I from the three available study cohorts was 5.85% and, thus, more than 1% higher compared to Italy. This north-south discrepancy was evident in the Stark map, where countries such as Denmark, Norway or Sweden, in particular, showed markedly higher n3 bio-status compared to the poor n3 bio-status in countries such as Italy and Greece. In Scandinavian countries, such as Norway and Sweden, in particular, n3 PUFA-rich fish such as salmon and herring are preferred. In

Germany, where fish consumption was 14.1 kg/capita/y in 2020, fatty cold-water fish such as salmon and herring are also among the preferred fish [31].

Low consumption of (fatty) fish could also be a reason for low mean O3I levels in the US (weighted average mean: 5.44% without Alaska cohort) and Canada (4.5%). According to the United States department of agriculture (USDA), total fish and shellfish intake in the US in 2018 was 4.38 kg/capita/y (adjusted for loss) [35] and, thus, less than one serving/wk. This was confirmed recently in the VITAL study, a US nationwide study with more than 20,000 US adults, in which median fish consumption was 1.5 servings/wk [36]. In the CHMS cohort, which is representative for the Canadian population, most individuals did not consume fish twice a week (88%) – out of which one meal was fatty fish – and did not take n3 supplements (91%) [37]. The authors also found that consuming fish twice a week or more (including at least 1 meal of fatty fish) was associated with higher O3I than consuming less fish [37]. Possible reason for the higher mean O3I in US cohorts, compared to Canada, despite similarly low fish consumption, could be the higher average age; the CHMS cohort in Canada covers an age range of 20-79 y, while the age range in the various US cohorts was between 40 and 66 y. It is well known that the O3I slightly increases with age [38]. The possible reasons for an O3I increase with age are diverse and probably related to a higher EPA, DHA and ALA intake from food (not supplements) [11,27]. Unfortunately, the amount of EPA and DHA consumed by the individuals of different age groups in the current cohorts are unknown.

Taken together, our data show that, other than Japan, South Korea and Alaska, where O3I values were desirable, and Spain with moderate status, levels were low in the US, Canada, Germany, and Italy. For the US and Canada in particular, the low O3I documented here is an improvement over the more dire ‘very low’ categorization from Stark et al. [28]. Given that a large number of participants from the US were included, and that the Canadian data were from a national survey, our categorization is likely to reflect the true situation. This is not to say that levels are “healthy” because “low” levels in these countries (and Italy and Germany) are still unsatisfactory. Observational and cross-sectional studies showed that lower O3I levels in RBCs are associated with increased risk for total mortality [9], ischemic stroke [9], reduced brain volume [39], impaired cognition [40], progression to dementia [41], postpartum depression [42] and psychiatric diseases [43]. Although an O3I >8% can clearly be achieved by eating fish alone (e.g., Japan, South Korea), for individuals in Western cultures where fish intake is traditionally low, simply *recommending* increased fish consumption has recently been shown to be an ineffective strategy for markedly improving the O3I [44]. Thus, in practice, an O3I >8% can only be achieved in western cultures by taking n3 PUFA supplements as well as through the consumption of n3 fortified foods [45]. In the VITAL study, which showed a median basal O3I of 4.84%, the median O3I achieved after 1 year of supplementation with 1 g/d of EPA + DHA was 7.82%, whereas 38% of the probands achieved an O3I >8% [46].

Most of the O3I US data were derived from clinical laboratory databases. As the data were not derived from official national surveys, they may not be representative of healthy US adults. However, a recent study (Wolin et al. 2015) found that biomarkers such as cholesterol or glucose in clinical laboratory data were essentially consistent with those

typically measured in adults in US-nationwide surveys. These considerations suggest that these clinical laboratory cohorts are generally representative of the (adult) US population. It is noteworthy that the mean O3I values of the clinical laboratory cohorts from the US largely agree with observational cohorts, as well as the weighted average mean of all US cohorts (excluding Alaska). However, it should also be noted that the cohort studies themselves are not strictly representative of the US population.

High ALA levels in the Canadian cohort may be related to high intake of ALA-rich linseed and canola oil in Canada [20]. The finding that high ALA levels may coincide with low O3I levels suggests that EPA and DHA bio-status is independent of ALA bio-status. Indeed, supplementation with ALA does not increase the O3I [47]. The high ALA levels in South Korea may be related to the high intake of perilla seeds (mainly perilla seed oil), and linseed oil [48]. The mean intake of ALA among Koreans (>1 y) was 1.26 g/d, based on the Korea National Health and Nutrition Examination Survey (KNHANES) 2013-2017 [49].

Trans FA levels varied considerably across these seven countries. The tendency toward decreasing total trans FA is reflected in "younger" studies (i.e., samples taken within the last 10 y) in comparison to “older” studies. For example, total trans FA level in the 1993 WHI-MS study was 2.70%, compared with 1.4% in the VITAL study in which samples were collected between 2011 and 2014. Trans FA levels in foods have decreased significantly in the last decades in many countries due to mandatory regulations and voluntary measures [50-52]. Declining RBC levels of trans FA have been linked with decreasing rates of ischemic heart disease in the US [52].

Finally, oleic acid levels were higher in the two Mediterranean countries – Italy and Spain – than in the other cohorts. This is likely due to the common use of oleic acid-rich olive oil in this region.

Strengths and limitations

This is the first study to compare the long-chain n3 PUFA bio-status in different countries derived from a uniform laboratory method. The use of the O3I method in all of these cohorts represents the greatest strength of the study. For some countries – especially the US – the database is very large.

However, the study has a number of potential limitations. The countries from which the study data originate are exclusively within so-called western world. Unfortunately, for many other countries there are insufficient data or no data at all. With the exception of the Canadian cohort, the study cohorts are not formally representative of their populations. Even if most of the cohorts were balanced in terms of sex, the mean age range of 40 to 68 y makes these data more reflective of older adults. As O3I is typically higher in older people [38], our findings cannot simply be extrapolated to younger (or older) people in the respective countries. Given the nature of the data used here (typically aggregated, not individual level), stratification by age and sex could be undertaken. Finally, the cohorts did not have uniform health status. Some cohorts consisted of CDH risk patients, and others had a high proportion of metabolically unhealthy people despite their otherwise, generally healthy status.

5. Conclusion

Due to the importance of long-chain n3 PUFAs for maintaining health and disease-prevention, countries undertaking national health surveys should emulate the example of Canada and use the O3I [53]. This would allow the identification of countries and regions with clinically concerning n3 PUFA levels. Despite several limitations, the 7-countries omega-3 study is a first step towards establishing a systematic worldwide n3 status database based on a uniform analytical method.

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Abbreviations:

ALA	alpha Linolenic Acid
ARA	Arachidonic Acid
BPRHS	Boston Puerto Rican Health Study
CHMS	Canadian Health Measures Survey
DHA	Docosahexaenoic Acid
EPA	Eicosapentaenoic Acid
EPIC	European Investigation into Cancer and Nutrition
ERA JUMP	EBCT and Risk Factor Assessment among Japanese and US Men in the Post World War II Birth Cohort

GISSI – HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca – Heart Failure
GOCADAN	Genetics of Coronary Artery Disease in Alaskan Natives
ISSFAL	International Society for the Study of Fatty Acids and Lipids
KNHANES	Korea National Health and Nutrition Examination Survey
LA	Linoleic Acid
LURIC	Ludwigshafen risk and cardiovascular health study
NHANES	National Health and Nutrition Examination Survey
O3I	Omega-3 Index
PREDIMED	PREvención con DIeta MEDiterránea Trial
RCT	Randomized Controlled Trial
VITAL	Vitamin D and Omega-3 Trial
VMF	VitaMinFemin study
WHI-MS	Women's Health Initiative Memory Study

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Table 1:

Mean Omega-3 Index values (% EPA + DHA of total fatty acids in RBC membranes) in cohorts of observational studies or a national survey from different countries worldwide.

	RCT	Observational studies					National Survey
Full RBC FA Profile Published?	**Yes**	**No**	**No**	**Yes**	**No**	**Yes**	**Yes**
Study Ref	[54]	-	-	[16]	-	[55]	[37]
Cohort	GISSI – HF	Pooled controls	ERA JUMP	PREDIMED	LURIC	VMF	CHMS
Country	Italy	Korea	Japan	Spain (Barcelona)	Germany	Germany	Canada
n	461	2,403	262	198	3,259	446	4,025
Males	77%	45%	100%	52%	70%	0%	50%
Subjects	Heart Failure	Healthy	Healthy	CVD Risk Factors	CHD	Healthy	Healthy
Sampling Date	2002-2005	2005-2017	2002-2006	2007-2009	1997-2000	2013-2015	2012-2015
Age (years)	67	61	45	66	63	49	20-79
C16:0	23.5%	24.0%	23.7%	22.5%	21.9%	22.6%	23.5%
C16:1n7t	0.13%	0.18%	0.07%	-	0.15%	-	0.17%
C16:1n7	0.76%	1.07%	0.43%	0.53%	0.48%	0.43%	0.35%
C18:0	16.3%	17.5%	16.9%	14.3%	17.2%	16.5%	17.8%
C18:1t	0.40%	0.54%	0.41%	-	0.60%	-	0.27%
C18:1n9	18.9%	13.5%	16.5%	17.6%	14.9%	15.9%	14.2%
C18:2trans	0.13%	0.33%	0.17%	-	0.21%	-	0.15%
C18:2n6	11.8%	12.0%	12.7%	13.4%	11.2%	11.6%	13.2%
C18:3n6	0.15%	0.16%	0.17%	0.12%	0.10%	0.09%	0.10%
C20:1n9	0.30%	0.25%	0.24%	0.30%	0.24%	0.29%	-
C18:3n3	0.10%	0.39%	0.26%	0.17%	0.12%	0.17%	0.29%
C20:2n6	0.28%	0.36%	0.25%	-	0.26%	0.22%	-
C20:3n6	1.79%	1.29%	1.36%	1.93%	1.76%	1.74%	1.86%
C20:4n6	13.9%	12.5%	11.7%	16.5%	16.5%	15.5%	14.7%
C24:0	0.55%	0.32%	0.24%	-	0.80%	0.85%	-
C20:5n3	0.55%	1.88%	2.08%	0.94%	0.76%	0.82%	0.76%
C24:1n9	0.75%	0.32%	0.14%	0.56%	0.76%	0.86%	-
C22:4n6	2.60%	2.10%	1.79%	-	3.24%	2.97%	2.96%
C22:5n6	0.59%	0.45%	0.33%	-	0.64%	0.64%	0.44%
C22:5n3	1.61%	2.63%	2.53%	1.81%	2.44%	2.47%	2.43%
C22:6n3	4.21%	7.38%	7.50%	6.09%	5.07%	4.66%	3.76%
Omega-3 Index	4.75%	9.26%	9.58%	7.05%	5.84%	5.49%	4.50%
Total Trans	0.66%	0.88%	0.65%	-	0.96%	-	0.59%

GISSI – HF, Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca – Heart Failure; ERA JUMP, EBCT and Risk Factor Assessment among Japanese and US Men in the Post World War II Birth Cohort; PREDIMED, PREvención con DIeta MEDiterránea trial; LURIC, Ludwigshafen risk and cardiovascular health study; CHMS, Canadian Health Measures Survey; VMF, VitaMinFemin study.

Table 2:

Mean Omega-3 Index values (% EPA + DHA of total fatty acids in RBC membranes) in cohorts of observational studies or clinical labs from the United States.

	Observational studies						Clinical laboratories			
Full RBC FA Profile Published?	**No**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**
Study Ref	[56]	[12]	[57]	-	[58]	-	[38]	-	-	-
Cohort	GOCADAN	Framingham Offspring	BPRHS	Framingham Gen3	WHI-MS	VITAL	Health Diagnostic Laboratory	Cooper Clinic	Prism	Salveo
City (Region)	Nome, AK	Boston, MA	Boston, MA	Boston, MA	Nationwide	Nationwide	Nationwide	Nationwide	Nationwide	Nationwide
n	707	3,216	1,482	3,813	7,303	1,929	86,012	14,199	8,321	29,311
Males	45%	45%	27%	47%	0%	49%	45%	64%	NA	NA
Subjects	Healthy	Healthy	Healthy	Healthy	Healthy	Healthy	Mixed	Healthy	Mixed	Mixed
Sampling Date	2000-2004	2005-2008	2004-2009	2002-2005	1993	2011-2014	2011-2012	2009-2012	2015-2018	2016-2019
Age (years)	50	66	57	40	63	67	66	49	64	55
C16:0	20.9%	21.3%	21.9%	21.1%	21.0%	21.3%	21.3%	22.2%	21.8%	21.8%
C16:1n7t	0.10%	0.17%	0.13%	0.18%	0.16%	0.10%	<0.10%	0.10%	0.10%	0.10%
C16:1n7	0.80%	0.36%	0.51%	0.47%	0.47%	0.30%	0.29%	0.20%	0.20%	0.30%
C18:0	13.7%	18.1%	17.5%	16.8%	16.7%	17.4%	18.0%	17.9%	18.2%	17.6%
C18:1t	1.60%	1.70%	1.03%	0.68%	2.11%	1.0%	0.66%	0.80%	0.60%	0.50%
C18:1n9	15.4%	13.9%	14.5%	14.3%	14.1%	14.4%	14.2%	14.2%	14.2%	14.7%
C18:2trans	0.40%	0.26%	0.16%	0.16%	0.43%	0.30%	0.25%	0.30%	0.10%	0.10%
C18:2n6	17.5%	11.1%	12.3%	13.8%	11.9%	12.2%	11.4%	12.0%	11.9%	13.1%
C18:3n6	0.10%	0.08%	0.15%	0.15%	0.17%	0.10%	<0.10%	0.10%	0.10%	0.10%
C20:1n9	0.20%	0.27%	0.21%	0.22%	0.23%	0.30%	0.28%	0.20%	0.20%	0.20%
C18:3n3	0.20%	0.19%	0.13%	0.17%	0.16%	0.20%	0.15%	0.10%	0.10%	0.20%
C20:2n6	0.20%	0.28%	0.31%	0.30%	0.30%	0.30%	0.30%	0.30%	0.30%	0.30%
C20:3n6	1.70%	1.60%	1.83%	1.87%	1.76%	1.80%	1.69%	1.70%	1.70%	1.70%
C20:4n6	12.4%	16.8%	16.6%	16.2%	16.7%	16.3%	16.0%	15.8%	15.9%	15.2%
C24:0	0.40%	0.45%	0.58%	0.53%	0.36%	0.70%	1.21%	0.50%	0.70%	0.60%
C20:5n3	2.20%	0.72%	0.43%	0.67%	0.69%	0.63%	0.80%	0.80%	0.90%	1.06%
C24:1n9	0.50%	0.42%	0.54%	0.48%	0.29%	0.60%	1.16%	0.40%	0.60%	0.60%

	Observational studies						Clinical laboratories			
Full RBC FA Profile Published?	**No**	**Yes**	**No**	**No**	**Yes**	**No**	**No**	**No**	**No**	**No**
C22:4n6	1.30%	3.79%	3.70%	3.74%	3.97%	3.50%	3.54%	3.70%	3.60%	3.10%
C22:5n6	0.40%	0.66%	0.79%	0.71%	0.79%	0.60%	0.61%	0.60%	2.70%	2.60%
C22:5n3	2.50%	2.73%	2.00%	2.54%	2.49%	2.50%	2.66%	2.70%	0.70%	0.60%
C22:6n3	6.80%	4.82%	3.95%	4.22%	4.48%	4.39%	4.50%	4.70%	4.77%	4.84%
Omega-3 Index	9.10%	5.54%	4.37%	4.90%	5.17%	5.02%	5.30%	5.50%	5.68%	5.95%
Total Trans	2.10%	2.10%	1.19%	1.03%	2.70%	1.39%	0.91%	1.20%	0.82%	0.77%

NA, not available

GOCADAN, Genetics of Coronary Artery Disease in Alaskan Natives; BPRHS, Boston Puerto Rican Health Study; VITAL, Vitamin D and Omega-3 Trial; WHI-MS, Women's Health Initiative Memory Study.

Prostaglandins Leukot Essent Fatty Acids. Author manuscript; available in PMC 2023 August 21.