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

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ABSTRACT

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

1. Introduction

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

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

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

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

2. Materials and methods

2.1. Data extraction

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

2.2. Data manipulation

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

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

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

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

3. Results

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

4. Discussion

This analysis was undertaken to estimate how risk for fatal CHD