Omega-3 Index: From biomarker to risk marker to risk factor

William S. Harris, PhD
Professor, Sanford School of Medicine, University of South Dakota
Founder, OmegaQuant Analytics, Sioux Falls, South Dakota
Omega-3 Index

A measure of the amount of EPA+DHA in red blood cell membrane phospholipids expressed as the percent of total fatty acids


There are 64 fatty acids in this model membrane, 3 of which are EPA or DHA

\[
\frac{3}{64} = 4.6\%
\]

Omega-3 Index = 4.6%
OMEGA-3 INDEX AND RISK FOR CARDIOVASCULAR DISEASE

Selecting Omega-3 Index Targets

Omega-3 Index Target

Recommend ~1500 mg of EPA + DHA

Recommend ~750 mg of EPA + DHA

All good: Recommend no change

Red Blood Cell EPA+DHA (% of total fatty acids)

Undesirable <4%
Intermediate 4%-8%
Desirable 8%-12%

Docosahexaenoic acid status of preterm infants at birth and following feeding with human milk or formula

Susan E Carlson, PhD. Philip G Rhodes, MD, and Mitzi G Ferguson, MD

ABSTRACT  The docosahexaenoic acid (DHA) status of preterm infants (< 32 wk gestation) was measured as the molar percent of DHA in individual red blood cell phospholipids: 1) in cord venous blood immediately following delivery, 2) after infants were receiving > 60 kcal·kg·day of energy from oral-gastric feedings, and 3) at a mean of 7 wk later. Infants on full feeding received either preterm human milk or formula. The DHA concentration of all phospholipid classes declined between birth and the time at which enteral feedings constituted the primary source of energy. Subsequent feeding with preterm human milk increased the molar percent of red blood cell phospholipid DHA, while DHA declined further in infants fed formula. Infants fed human milk compared to those fed formula had a significantly higher molar percent of DHA in all red blood cell phospholipids studied.  Am J Clin Nutr 1986;44:798–804.

KEY WORDS  Human milk, formula, preterm, infants, docosahexaenoic acid, arachidonic acid
The Omega-3 Index: A validated biomarker of omega-3 intake


Only group to exceed 8% on average
Group meeting AHA goal

State of the Science 2020
Omega-3 Index: A *risk* marker for cardiovascular disease
<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
<th>Satisfied by the omega-3 index?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proof of concept</td>
<td>Do novel marker levels differ between subjects with and without the outcome?</td>
<td>Yes</td>
</tr>
<tr>
<td>Prospective validation</td>
<td>Does the novel marker predict development of future outcomes in a prospective cohort or nested case-cohort/case-cohort study?</td>
<td>Yes</td>
</tr>
<tr>
<td>Incremental value</td>
<td>Does the novel marker add predictive information to established, standard risk markers?</td>
<td>Uncertain; prediction is independent of standard risk markers</td>
</tr>
<tr>
<td>Clinical utility</td>
<td>Does the novel risk marker change predicted risk sufficiently to change recommended therapy?</td>
<td>Yes, given the safety and low cost of treating</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td>Does use of the novel risk marker improve clinical outcomes, especially when tested in a randomized clinical trial?</td>
<td>Yes (in secondary analyses of RCTs)</td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?</td>
<td>Yes, given the low cost of testing and treating</td>
</tr>
</tbody>
</table>

Omega-3 Index: A risk factor for cardiovascular disease (and beyond!)
| Criterion                | Description                                                                 | Satisfied by the omega-3 index? |
|-------------------------|                                                                           |                                |
| Temporal Relation       | Exposure to the factor always precedes the disease.                       | Yes                             |
| Strength                | The stronger the association, the more likely the causal relation.         | Yes                             |
| Dose-Response Relation  | The greater the exposure, the lesser the incidence (or prevalence) of the disease. | Yes                             |
| Consistency and Coherence | The association between the factor and the disease is consistent across different study designs, using different analytical methods, endpoints and populations. In addition, data from several disciplines (epidemiology, biochemistry, randomized trials, cell culture, animal models, etc.) harmonize. | Yes, but more studies always needed |
| Plausibility            | The association between the factor and the disease is reasonable given the current understanding of biology. | Yes                             |
| Experiment              | **Changing exposure to the factor changes the incidence of the disease.**   | Yes                             |
| Specificity             | A specific factor is associated with a specific disease.                   | No – linked to several disease outcomes |

OMEGA-3 INDEX AND ACUTE CORONARY SYNDROMES (768 CASE-CONTROL PAIRS)

Those with an Omega-3 Index >8% were 70% less likely to be an ACS patient than those with an Index <4%

Multivariable logistic regression model including: age; race; gender; history of diabetes mellitus, hypertension, hyperlipidemia and/or myocardial infarction; a family history of coronary artery disease; and LDL-C, HDL-C, and triglycerides.
META-ANALYSIS: OMEGA-3 INDEX AS A PREDICTOR OF RISK FOR FATAL CORONARY HEART DISEASE

(10 STUDIES WORLDWIDE - OVER 27,000 SUBJECTS)

Does the marker predict development of future outcomes in a prospective cohort studies?

Risk for fatal CHD was 35% lower in persons with an Omega-3 Index of 8% compared with those with an Index of 4%
Multivariable-adjusted risk for death from any cause between age 70 and 85 in 6501 post-menopausal women was 31% lower with an Omega-3 Index of >8% vs <4%.

Changing exposure to the factor changes the incidence of the disease.
OMEGA-3 INDEX

Validated biomarker of omega-3 intake
Better than dietary intake questionnaire
More stable than plasma omega-3 levels

Satisfies 6 of 7 AHA Criteria as a Risk Marker
Incremental value needs further study

Satisfies 6 of 7 Hill Criteria for a Causal (Risk) Factor
Fails to be “specific” for heart disease (but that’s not a weakness)
Omega-3 Index – Biomarker to Risk Factor

Conclusions

• Higher Omega-3 Index levels are clearly associated with better health
• The primary way to raise the Omega-3 Index is by eating more “oily” fish (salmon, herring, sardines, albacore tuna, etc.)
• Omega-3 (EPA+DHA) capsules can also raise the Omega-3 Index