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Craddock JC, Neale EP, Probst YC, Peoples GE. Algal supplementation of vegetarian eating patterns improves plasma and serum docosahexaenoic acid concentrations and omega-3 indices: a systematic literature review. J Hum Nutr Diet. 2017 Dec;30(6):693-699.

What We Know, Think We Know, or Are Starting to Know

We know we love some omega-3 research around here. But as essential fatty acids, the importance of adequate intake of these fats in the diet cannot be overstated. Within this literature, however, lingers a burning question: what about dietary patterns and practices that do not include fish or direct sources of eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]?

With the increasing trends in vegan, and vegetarian diets that may exclude fish, this question has relevance for both individual health and for public health. The main argument against having a direct source of EPA and DHA is that both fatty acids can be synthesised from the plant-derived precursor fatty acid, alpha linolenic acid [ALA], and that any additional intakes would be a *"functionally irrelevant surplus"* [(1)]. We' ll come back to this point.

We know that in *Sapiens*, the synthesis of EPA and DHA from ALA is minimal, with an average conversion of 8-12% to EPA and ~1% to DHA [(2)]. We also know that there are sex differences in rates of conversion, with women converting significantly higher levels of ALA to EPA and DHA of 21% and 9%, respectively, while men only convert around 0.3-8% of ALA to EPA and <1% to DHA [(3)].

But what of people not consuming any, or any sufficient, direct sources of EPA/DHA? We know that population research shows that individuals consuming vegetarian diets excluding fish, vegan diets, or omnivores not consuming fish, have lower EPA/DHA status [(4–6)].

There are two questions we can posit here:

1. Compared to only consuming ALA, would a direct source of EPA/DHA improve levels of these fatty acids in the body?
2. If 'Yes' , is this actually needed for health outcomes?

Within the marine ecosystem, the primary producers of EPA and DHA are microalgae [(7)]. Plankton feed on algae, and fish feed on plankton. Thus, the chain of who eats who goes like this: Algae>Plankton>Salmon>Sapien. In world where sustainability issues and ethical considerations are front-and-centre in the nutrition debate, what would happen if we cut the middle fish out of the equation?

The Study

The researchers conducted a systematic review of studies investigating the effects of algae-based DHA supplementation on biomarkers of DHA status in vegetarian and vegan diets. To be included in the systematic review, a study had to meet the following inclusion criteria:

- The study used an algae-based DHA supplement;
- Participants were following a vegetarian diet excluding fish or vegan diet;
- The study measured biomarkers of DHA status, i.e., red blood cells [RBC], plasma, or the omega-3 index*.

*Geek Box: Omega-3 Index

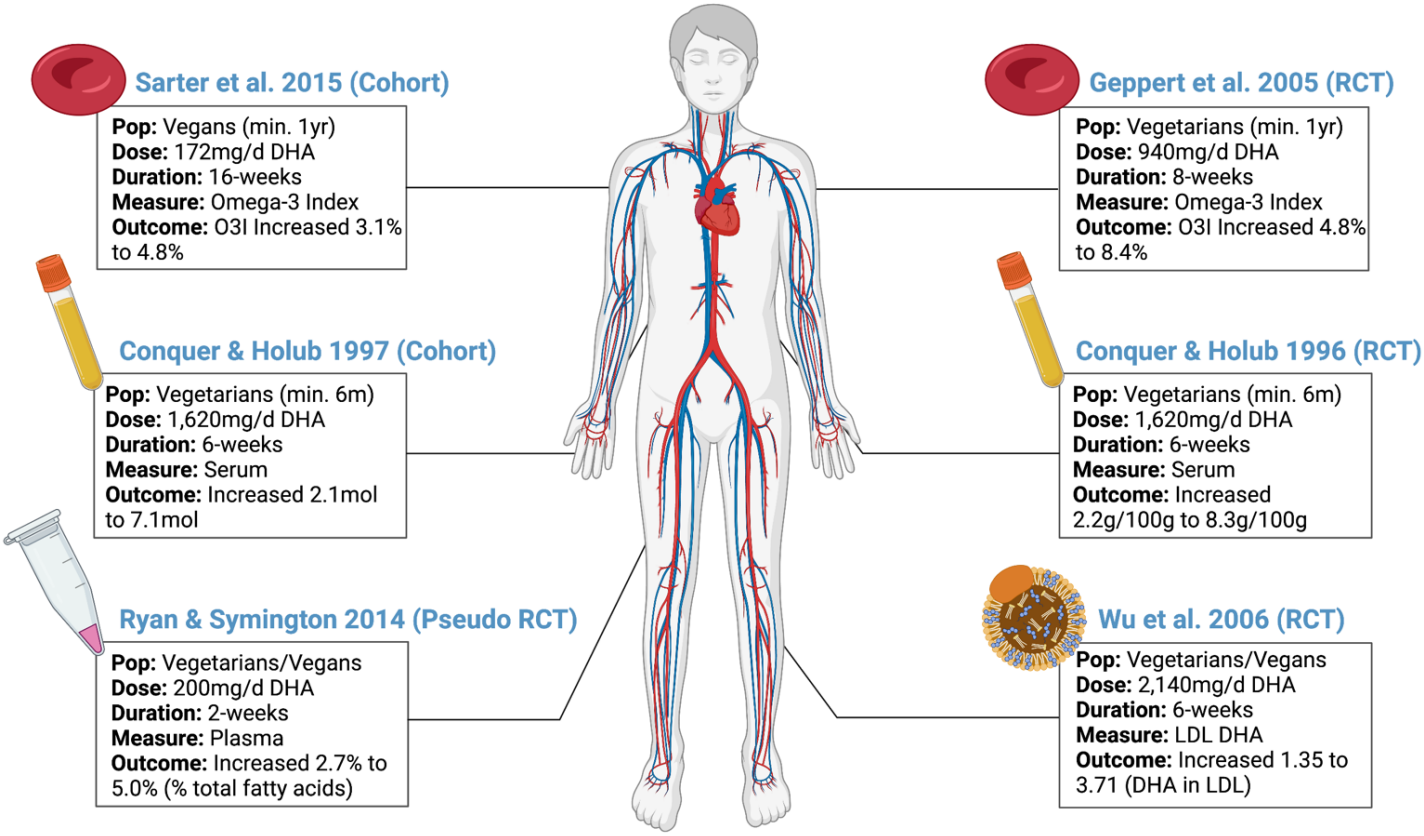
The question over what to measure to obtain reliable measures of DHA + EPA levels has been examined in numerous studies, ultimately leading to an argument in favour of red blood cell [RBC] measures. The Omega-3 Index was first proposed in 2004 and is calculated as the sum of DHA + EPA in RBCs, expressed as a percentage of the total fatty acids in the RBC measure. Because DHA is the predominant omega-3 fatty acid in membrane phospholipids, DHA makes up the majority of the Index. This is not to suggest that EPA does not have important roles, however, it may mean that looking at EPA alone would not yield any meaningful findings. The Omega-3 Index has been shown to be a robust predictor of cardiovascular disease. In addition, the Omega-3 Index appears to be stable and not easily altered by a given meal high in DHA + EPA, thus is a more reliable biomarker that is not easily influenced by recent dietary intake alone. An attractive feature of the Omega-3 Index is that the analytical laboratory procedure has been standardised, which means the measure should be reproducible across populations: the standardised method is known as the HS-Omega-3 Index®. Of note, since the use of the standardised index populations in Korea and Japan - with generally higher fish consumption – have exhibited significantly higher indices than American populations. Lower Omega-3 Index is also quite consistently associated with worse outcomes compared to higher levels. So, what is 'low' or 'high' for the Omega-3 Index? It appears that <4% is associated with worse health outcomes, particularly when compared to populations with levels of >8%. Populations in Scandinavia and Japan exhibit the highest Omega-3 Index levels.

Results: 6 studies met the inclusion criteria and were systematically reviewed on the study design, population, dose of DHA used, duration of study, number of participants, age of participants, and measure of DHA status.

The doses of DHA ranges from 172mg/d to 2.14g/d. One study had participants who were exclusively vegan, while the remainder were vegetarian or a mix of both vegetarians and vegans. The sample sizes of the studies were, from lowest to highest, $n = 12$, $n = 20$, $n = 24$, $n = 25$, $n = 46$, and $n = 108$.

The studies used a range of measures for DHA status, with 2/6 using the Omega-3 Index, and the others using serum, plasma, or measured DHA in low-density lipoproteins [LDL].

The details of the 6 included studies are summarised in the infographic, below.



The Critical Breakdown

Pros: The study is the most recent synthesis of evidence on this important research question. The research question was focused, and the inclusion criteria clearly defined. The review was pre-registered, and relevant databases were searched up to the year prior to publication. All relevant study details were included in the summary of included studies.

Cons: The question begs why the researchers did not conduct a meta-analysis of the studies, but to be fair to the researchers it likely that the studies varied too much in the dose of supplement, the duration of trial, and the measurement of DHA. 4/6 studies were less than two months duration and used biomarkers, like serum or plasma, which may not be as good a reflection of DHA status compared to RBCs [more under ***Key Characteristic***, below]. The studies also had small sample sizes, with the largest being 108 participants.

Key Characteristic

As a systematic review, we are left to compare and contrast between the included studies to parse together some coherent conclusions. In this regard, a primary distinction can be made between those studies [2/6] which used the Omega-3 Index, and those which measured serum of plasma [3/6]. This distinction is important because it relates to DHA metabolism. If you have yet to watch the Research Lecture discussing nutritional biomarkers, I recommend you watch that, and you' ll see that different tissue compartments correspond to different reflections of dietary intake. Generally, RBCs reflect more stable dietary intake over the previous ~3-months, while plasma or serum may only reflect the previous 2-3 days [8]. Further, the half-life of DHA in plasma is as short as two minutes [9]. In contrast, the Omega-3 Index primarily reflects DHA status in RBCs, and is a much more robust biomarker of DHA status that is physiologically relevant (10). Given how short the interventions were that measured serum or plasma [1 study was 2-weeks, the others were 6-weeks], it is possible that the changes in DHA levels in serum/plasma in those studies reflected only a transient effect of supplementation, an effect which would likely have disappeared rapidly after cessation of the supplement.

Interesting Finding

Of the included studies, the Sarter et al. [11] paper provides the most interesting insight into the effects of DHA supplementation in non-fish consumers. The study was conducted exclusively in vegans, used the Omega-3 Index [O3I] as a measure before and after, had participants with <4% O3I and was conducted over 16-weeks, i.e., a long enough time-course to see potential changes in RBC omega-3 status.

At baseline, vegans had an average O3I of 3.7%, while 64% had <4% and 27% were <3%. This is important because the wider research using the O3I indicates that <4% is associated with adverse cardiovascular and neurological outcomes [12,13]. After identifying vegans with a baseline O3I Index of <4%, they supplemented them with DHA and achieved a final level of 4.8%.

The study also compared the Omega-3 Index of vegans to a study which measured levels in US troops in Iraq [omnivores]; this group also had levels <4% [11]. This serves to highlight that people may have low Omega-3 Index levels independent of dietary pattern. Nevertheless, the study showed that algae-based preformed DHA supplementation is effective at increasing the O31 in people following a vegan diet.

Relevance

The present systematic review ultimately highlights the lack of quality evidence in this area. However, there are some lines of evidence we can draw on to derive some conclusions. The Sarter et al. study was one of the two best quality studies included in this systematic review, the other being the study by Geppert et al. [14], which was conducted in 108 vegetarian participants with a baseline of 4.8% O3I, and achieved an O3I of 8.4% after 8-weeks supplementation with 940mg/d DHA.

Immediately these two studies tell us something: that there is a dose-response between supplemental DHA and increases in the O3I, which is consistent with previous research [15]. And that higher doses of DHA can achieve levels of the O3I associated with beneficial health outcomes in a shorter time frame. This is important because, while the Sarter et al. study did increase O3I levels, it was a paltry increase overall and the final measured O3I level was still low by reference to the wider research on the O3I [12,13].

There are potentially important implications for people excluding direct sources of DHA in the diet, irrespective of dietary pattern, because it is clear from the research that ALA intakes of anything from 2g/d to 15g/d have no effect on DHA levels [2,16,17]. We have covered a study that found no effect of 14g/d ALA supplemented through linseed oil on EPA and DHA concentrations in participants with low EPA and DHA status in a previous Deepdive. Of particular note, supplementing with EPA will not even increase DHA status [16].

So we know that neither ALA or EPA are sufficient to increase DHA status in the body, which appears to be only responsive to direct preformed DHA sources. The next question is whether whatever low DHA levels are present absent any direct source from dietary intake are sufficient. Indeed, this is argued in the research, that in people not consuming direct sources of DHA, DHA levels in the body stabilise at a low plateau and provide sufficient levels for physiological function [1,5]. But this arguments fails to account for:

1. The fact that brain DHA levels may be the most important determinant, and it may take years for cognitive impairment from lack of direct DHA intake to manifest [9,18];
2. The fact that the O3I primarily reflects DHA status, and compared to an O3I of <4%, >8% is consistently associated with better cardiovascular and neurological health outcomes [12,13];
3. The fact that research in vegan and vegetarian populations to date has only looked at changes in omega-3 status as an outcome, not health outcomes like disease risk.

It requires a lot of motivated reasoning to conclude that certain dietary patterns, in particular vegan or vegetarian diets, are somehow exempted from the wider research consistently demonstrating greater DHA status is associated with improved health outcomes compared to less, because they are otherwise healthy dietary patterns. We lack the long-term data to make that conclusion.

Application to Practice

And so the question begs, to supplement or not to supplement with a direct source of DHA? My personal inclination based on this data currently is that the evidence indicates that more is preferable to less, and some is preferable to none.

Put it this way: take two individuals both following a vegan diet, both following a very healthy iteration of a vegan diet with plenty of ALA, veg, fruits, fibre, etc. One consumes no direct DHA, the other consumes a direct source of DHA as an algae-based supplement. Which has better outcomes? We don' t have that data, so we are left with a hypothesis. My hypothesis would be that the one taking DHA would have better long-term outcomes, particularly for neurological health as vegan diets are good for cardiovascular health anyway. To quote from the Sarter et al. paper:

"The consistency of the epidemiological findings suggests that a lifetime DHA insufficiency may put vegans at increased risk for cognitive dysfunction."

Until we have data to the contrary, this is a risk I' m not willing to recommend. Given everything we know about the critical role of DHA in the brain and central nervous system, an algae-based supplement might just be as prudent as B12 supplements for people following any dietary pattern that excludes direct sources of DHA.

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