

Review of *JAMA Cardiology's* 2018 “Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks”



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- ▶ Major books include *Inflammation Mastery 4th Edition* (and any later versions) printed also in separate and progressive volumes as *Textbook of Clinical Nutrition and Functional Medicine* (2016), with excerpts published as *Brain Inflammation* (2016), *Human Microbiome and Dysbiosis in Clinical Disease* (2015); anticipated new books include *Deciphering the Gut-Brain Axis in Clinical Practice* (2018) from which *Autism, Dysbiosis, and the Gut-Brain Axis* (2017) has been prereleased.
- ▶ Peer-reviewed/independent publications include: *The Lancet.com*, *British Medical Journal (BMJ)*, *Annals of Pharmacotherapy*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics (JMPT)*, *Journal of the American Medical Association (JAMA)*, *Original Internist*, *Integrative Medicine*, *Holistic Primary Care*, *Alternative Therapies in Health and Medicine*, *Journal of the American Osteopathic Association (JOA)*, *Dynamic Chiropractic*, *Journal of Clinical Endocrinology and Metabolism*, *Current Asthma and Allergy Reports*, *Complementary Therapies in Clinical Practice*, *Nature Reviews Rheumatology*, *Annals of the New York Academy of Sciences*, and *Arthritis & Rheumatism*, the Official Journal of the American College of Rheumatology.

The video of this presentation is archived at ichnfm.org/jama2018n3, and the transcript in PDF format—which is considered the final and citable version—is archived at academia.edu/35935996; any corrections or updates will be made to the PDF file. The video contains citations which are not replicated in the PDF document; both the video and the PDF transcript should be reviewed for a complete representation of the information. This version was updated on **February 24, 2018**.

Introduction: “Hello, everybody. Dr. Alex Vasquez here with today's video, which is going to focus on reviewing *JAMA Cardiology's* 2018 article, “Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks.”¹ Let's begin by taking look at that recently published article right here. Again, this was published in *JAMA Cardiology*, January 31, 2018. That is only about two weeks ago, and the article has already had more than 100,000 views. Typically, when *JAMA* is going to publish an article against nutrition, they make the article available online and free, and that is certainly the case here. Again, title of this article, “Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks,” subtitled “Meta-analysis of Ten Trials Involving 77,000 Individuals,” almost 78,000 individuals.

Contextualization: In order to put this article in context, I am going to start by contextualizing the organization and the journal itself. I'll try to keep that relatively short so we can dive into the analysis of this article, but I do think that some contextualization is important because this journal is considered to be very authoritative. It's used by news services, and a lot of press releases certainly went out about this article, showing and stating basically that fatty acid supplementation from fish oil is of no use in the prevention of cardiovascular events.

Journal of the American Medical Association—*JAMA*—is notorious for publishing pro-drug and anti-nutrition articles. Big medical journals and organizations make multimillion dollar profits from their pro-drug stance, and they have a massive, inherent conflict of interest to publish pro-drug articles and anti-nutrition articles. One of the ways that this conflict of interest manifests is that drug companies will often buy a pro-drug article or an anti-

¹ Aung et al. Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks. *JAMA Cardiol* 2018 Jan 10.1001/jamacardio.2017.5205

nutrition article, and they'll often pay millions of dollars for those reprints. You can see that that was detailed here in an article by Richard Smith, former editor of the *British Medical Journal*. "Medical journals," he states, "are an extension of the marketing arm of pharmaceutical companies." (This article was published in *PLOS Medicine* in May of 2005 and is available online for free.²) These medical journals and organizations also publish pro-drug advertisements. That's another source of several million dollars in profits. They also endorse pro-drug treatment protocols, and that, of course, benefits the drug companies, and the drug companies then reciprocate by promoting pro-drug, pro-medical legislation, and that's how we end up with mandatory drug and vaccine protocols. You can see that all of this becomes a pro-drug vicious cycle.

Exemplary experience: I actually have personal experience with *JAMA*, which again I'm stating here is notorious for publishing pro-drug and anti-nutrition articles. This article that I'm going to talk about very quickly was published in July of 2004, "Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density and Plasma Lipids in Postmenopausal Women." Now just looking at the title of that article, which, of course, was also made available for free because *JAMA* likes to slam nutritional interventions, pretty much from the moment that I looked at the title of this article, I already knew that it was going to be *a study designed to fail*.

If you look at the title—"Effect of Soy Protein Containing Isoflavones on Cognitive Function, Bone Mineral Density and Plasma Lipids in Postmenopausal Women"—you see a lot of different variables, each of which requires different measurements and statistical analysis (etc) and probably they are not going to let soy protein with isoflavones actually win the day because this is a multimillion dollar market. And I am not talking about selling soy protein, I am talking about the drug market for each one of these clinical entities: 1) cognitive dysfunction, 2) osteoporosis, and 3) dyslipidemia. Those are multimillion and probably multibillion dollar markets. *JAMA* certainly is not going to publish an article favorable to nutrition, and that's what I suspected, and that turned out to be the case. In fact, this article was so bad, that I actually published a reply, and they were "kind enough" to publish my work; on the other hand, they pretty much destroyed the intention of what I had written.³ Again, I thought this article was rather ridiculous, so I wrote a reply, which *JAMA* decided to publish. However, they completely edited out any significant meaning from my letter. They reduced the word count by about 60%, and they took out what I consider to be the most significant part of my reply. And then I ended up getting this publication of only about four sentences in *JAMA*, instead of the other major paragraphs that actually contained what I consider to be the meat of the matter. Then the original authors were allowed to retrofit some data, which hadn't been published previously and which they then claimed maintained the validity of their research, and I have to say that I don't agree with that. If it had been *valid from the start*, they should have *published that data from the start*, **not retrofit their data** in reply to my truncated critique. As a result of all this, basically, the science was obscured, and it was done so for the purpose of maintaining pharmaceutical dominance, in my opinion.

Article review and critique: Let's get back to this article and take a look at it through a structured analysis, we might say. You've got the citation; you've got the design—meta-analysis of 10 trials with almost 78,000 people.



Context can reveal more than can content, just as appreciation of a constellation tells us more than does the location of a single star

"Context can be just as important as content. For example, whereas content may represent a single point of data, context reveals the pattern of events and occurrences and allows us to appreciate trends, significance, direction and intention."

Dr Alex Vasquez

² Smith R. Medical journals are an extension of the marketing arm of pharmaceutical companies. *PLoS Med* 2005 May doi.org/10.1371/journal.pmed.0020138

³ Muanza DN, Vasquez A, Cannell J, Grant WB. Isoflavones and postmenopausal women. *JAMA*. 2004 Nov 17;292(19):2337

Findings: "Randomization to omega-3 fatty acid supplementation (eicosapentaenoic acid with a dosage range of about 200 to 1,800 mg) has no significant associations with coronary heart disease death, although it did reduce the rate ratio, or the relative risk, by seven percentage points, nonfatal myocardial infarction reduced by three percentage points, or any coronary heart disease events, four percent reduction there. Their conclusion, "Supplementation with marine-derived," that's fish oil, "marine-derived omega-3 fatty acids for a mean of 4.4 years had no significant association with reductions in fatal or nonfatal coronary heart disease or any major vascular events." Basically, they're saying that fish oil does not provide benefit to reduce cardiac morbidity and mortality. That's basically their conclusion, and that's what got picked up in the news.

Now let's begin to look at the errors in this publication:

1. **Error by unjustified selective exclusion of data:** Again, error number one, that I have listed here, is unjustified selective exclusion of data. The authors state, "This meta-analysis included randomized trials that involved at least 500 participants and a treatment duration of at least one year." Well, if they're going to exclude a lot of data, they need to justify why they're doing that, not just say, "Hey, we decided and not to look at all this data." No scientific justification for this selection exists and, therefore, its inclusion must be questioned.

Again, one of their selection criteria was that all the studies that they were going to analyze had to have at least 500 participants, and my question is, well, where did they come up with that number? They provide no justification for that, so they were obviously *very selectively excluding a bunch of data* that they did not want to look at. My question is, "*why were the smaller studies, arguably easier to manage and perhaps with higher quality supplements, why were those excluded from this analysis?*" And I've also included a little more commentary at the bottom of the page. You can pause the video at any time if you want to read everything word for word. I'm going to try to maintain a little bit of momentum here.

2. **Error by non-therapeutic dosing:** Error number two that I'd like to talk about is inclusion of studies that employed non-therapeutic dosing. The authors state, "**No minimum daily dosage of EPA or DHA was specified.**" Now you should be raising your eyebrows at this point, and you should be asking yourself, "What's going on here?" **They had no minimum dose of the active components of the intervention that they're trying to analyze here? That is completely ridiculous.** Like I've stated previously with regard to vitamin D, sub-physiologic dosing is subtherapeutic. A lot of times in these nutritional studies, **they use low doses—sometimes subtherapeutic and subphysiologic doses—which obviously are not going to work**, in order to provide the desired outcome. We have to use therapeutic doses of drugs just like we have to use therapeutic doses of nutrients, if we want to see the outcome effected.

One of the ways that nutrition articles get shortchanged is the investigators use low doses, or they use insufficient duration of the study, so that the nutritional studies are shown to be inefficacious and that's exactly what they did here. In this case, by stating no minimum daily dose of EPA or DHA was specified, basically what they are saying is they had no standards for evaluating the appropriateness of the intervention and, therefore, of course, some studies will be published and analyzed within this meta-analysis showing inefficacy of the intervention when, in fact, it was a study design error, not an intervention shortcoming.

Stated more plainly here: **this article published in JAMA Cardiology is absurd for not emphasizing and including a minimum dose for the treatment being analyzed.** By comparison, **no meta-analysis of a drug treatment would be published if the authors ignored dosing or used "homeopathic" dosing levels** because everyone knows, in pharmacology and in medicine and in nutrition, that we expect to see a dose-response relationship and that this is, of course, of huge importance. Therefore, **to exclude this basic tenet of pharmacology—the dose-response relationship—is another big red flag that this review article is deviating from basic norms of science.** And you can see, I excerpted a clip from the article itself, "No minimum daily dose of EPA or DHA was specified," so that is a huge red flag that this is basically a nutrition witch hunt, and they are trying to look for data that makes fish oil supplementation look non-efficacious for the prevention of cardiovascular events. Let's continue this analysis.

Here, we are going to start looking at each of the individual studies that were analyzed in this so-called meta-analysis, again, not only published by *JAMA*, but published by the subspecialty journal, *JAMA Cardiology*. Let's see what we find from this table—see video for details. Number one, the majority of studies reviewed in this meta-analysis used inadequate subtherapeutic dosing, which, in my opinion, should be a minimum of 1800

milligrams of EPA and DHA. Most of the subjects in these studies were **not young, healthy** patients. These were already patients of older age, a lot of times with metabolic syndrome, obesity and cardiovascular disease. What is not appropriate is to use a *preventive* nutrition dose for something that requires therapeutic *intervention*. Lower doses of nutrients can be used for prevention, but for actual treatment, which applies to most of the subjects in these studies, for actual treatment, they needed higher doses for a variety of reasons. They have **inflammation**. They have **insulin resistance**. A lot of them were **obese**. They are going to need higher doses than what we would use in younger, healthy patients for disease prevention.

Again, I think, and I will show you the justification for this in just a moment, **the minimum dose here should be 1800 milligrams of combined EPA and DHA**—not one or the other, EPA and DHA together. If you look at the ingredients that were given to the subjects, you'll see that most of the studies did not meet this minimal criteria of 1800 milligrams per day of EPA and DHA. Now looking at each of the included studies: You can see that this study was inadequately dosed...you can see that this study was inadequately dosed. The following study reached 1800 milligrams, but they had no content of DHA, docosahexaenoic acid, which is the omega-3 fatty acid most important for changing the Omega-3 Index, which I will talk about in just a moment,

and also most anti-inflammatory for the cardiovascular system, which is basically how this is viewed these days. A lot of articles have stated that DHA is not simply important for the retina and the brain, but also it is the most important of these fatty acids for its cardioprotective benefits. In this particular study, the third one that we're looking at here, they used 1800 milligrams of EPA, but they had no DHA, so that is basically saying that **they excluded what a lot of specialists would consider to be the most important component**. Also, this particular study was performed with subjects exclusively from Japan, where they have a higher intake of omega-3 fatty

acids. Therefore, we could argue very reasonably and very easily that those patients would need higher interventional doses compared to those used in societies such as the United States, where people do not consume enough omega-3 fatty acids. If the baseline intake of omega-3 fatty acids is higher, then the interventional dose also needs to be higher. Whereas, again, if you're looking at subjects from the United States who typically do not consume omega-3 fatty acids in their diet, then a lower dose is actually going to have a better effect on those patients because they are starting from such a profound deficiency.

Here again, you see that this study used **absolutely inadequate dosing, 226 milligrams of EPA along with 150 milligrams of DHA**. That's absolutely, I would say, **infantile**. That's an appropriate dose for an infant, certainly not for an adult. Again, with this article, 840 milligrams, certainly not 1800 milligrams of EPA combined with DHA. This one got to one gram, and this one also was 840 milligrams.⁴ Of the studies that were analyzed in this supposed meta-analysis, **of the 10 studies that they analyzed, only three of them actually had what we would consider therapeutic dosages of the intervention that's being assessed here**. Again, right from the start, we can see that this article is probably going to be a witch hunt, trying to find data that makes fish oil

<p>DR VASQUEZ'S RESEARCH REVIEW</p> <p>Context</p> <p>Article & Corrections</p> <p>"Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks" JAMA Cardiology January 31, 2018</p>	<p>Errors in this publication</p> <p>2. ERROR by inclusion of studies that employed nontherapeutic dosing: "... no minimum daily dose of EPA or DHA was specified..."</p> <ul style="list-style-type: none"> ▶ Like I stated previously with regard to vitamin D, "subphysiologic dosing is subtherapeutic." (<i>Lancet.com</i> 2005 May, archived at ichnfm.org/d) ▶ This article published in <i>JAMA Cardiology</i> is absurd for not emphasizing/including a minimum dose for the treatment being analyzed. By comparison, no meta-analysis of drug treatment would be published if the authors ignored dosing, or used "homeopathic dosing" because everyone knows that dose-response relationships are of huge importance. Therefore, to exclude this basic tenet of pharmacology (ie, dose-response relationship) is another big red flag that this review article is deviating from basic norms of science. <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>or open-label control, with a sample size of at least 500 participants and a scheduled duration of treatment of at least 1 year. All eligible trials required use of supplements, but no minimum daily dose of EPA or DHA was specified. The prescrip-</p> </div>
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⁴ Author's production note: I think that during the recording of the video, due to the smaller dimension of the screen that I was using, I was misreading the 3 as an 8 and was therefore overestimating in my quick commentary the quantity of the fatty acids, effectively adding 500 mg to my quick math, during which I said both were slightly over 1,000 mg when in fact they were both below 1,000 mg, specifically at 840 mg.

look inefficacious for the prevention of cardiovascular events. Only three of the 10 studies actually meet criteria for being reasonable studies in terms of therapeutic dosages.

And, as I stated here: The **anti-nutrition bias of this publication is obvious** because the **authors and editors would never publish a review article using inadequate dosing of medication**. For example, let's say that the therapeutic dose of a drug is 10 units and several studies are performed using only three units of that drug, whether it's milligrams or grams or whatever. If they only use 30% of the effective dose, then what is the point in analyzing those studies? They're **underpowered therapeutically**. You can be sure that **any meta-analysis that looks at several studies, each of which is therapeutically underpowered, is going to reach the conclusion that the therapy doesn't work**. They do that all the time with nutrition studies, but *they would never do that with a drug study*. **They would never say, "The therapeutic dose of this drug is 10 units, we're only going to give 3, and then we're going to collect all those studies that were underpowered therapeutically, and we're going to do a meta-analysis. And, lo and behold, our conclusion is that this drug doesn't work."** They would never do that with a drug. They do it all the time with nutritional interventions. As I had stated previously, "Furthermore, most of these patients are **post-myocardial infarction**. They've got **systemic inflammation** and/or they are **obese** and, therefore, they need higher *interventional*—not *preventive*—doses. Again, only three of the 10 studies in this meta-analysis are appropriately therapeutically powered.

Let's continue the analysis. I'm going to stay with this major point that one of their errors was the inclusion of studies that employed non-therapeutic dosing. Let's look at this article for some context. This article was published in the well-respected specialty journal *Prostaglandins, Leukotrienes and Essential Fatty Acids* in 2017. "Supplementation with high-dose docosahexaenoic acid increases the omega-3 Index more than high-dose eicosapentaenoic acid." This is comparing DHA against EPA and the effect that either one of those will have on what's called the Omega-3 Index, which is a measure of omega-3 fatty acids in cell membranes. The Omega-3 Index correlates very strongly with cardiovascular disease and coronary mortality.

Typically, what's considered good is to have an Omega-3 Index of about 10%, somewhere between 8% and 12%, but let's just say 10% because, obviously, that's in the middle. Our goal for preventive purposes is to have an Omega-3 Index of approximately 10%. That means that of the fatty acids analyzed, roughly 10% of those are

Inappropriate/partial application of the pharmacologic model

What the authors of the poorly designed studies did was *partly* apply a pharmacocentric model to the study of nutrition, which can be considered a category error. Since fatty acids change outcomes by changing physiology after they have been incorporated into cell membranes, the researchers should have done all of the following in order to ensure that the intervention was pharmacologically efficacious: **① efficacious dose**: use an assuredly appropriate dose (eg, ~1800 mg of EPA and DHA), **② appropriate duration**: use an appropriate "loading duration" which for n3 fatty acids is a minimum of five months, **③ measure a biomarker for absorption, compliance, and incorporation**: they needed to measure the omega-3 index to test for absorption/incorporation and physiologic modification, eg, cell membranes. Pharmacologic efficacy is a prerequisite to clinical efficacy.

In the real world of clinical medical practice—to which this research attempts to appeal via its subject and (more overtly) via publication in the Cardiology specialty journal of the American Medical Association—initial doses are followed by patient-tailored adjustments to achieve the desired clinical effect (ie, dose-to-effect). The failed studies reviewed in this meta-analysis uniformly failed to dose to effect; very obviously then, these studies failed to accurately represent competent clinical practice by employing a "dose it and forget it" model, which is clinically incompetent. The researchers did this either via their own ignorance or in order to intentionally sabotage the outcomes of the studies.

In other words, they start with a clinical drug-dosing model of starting with dose X but they never dose-to-effect which is the real standard in clinical therapeutics. They are using only part of a pharmacologic dosing model (start with X dose) but never completing the other clinical part of that model, which is dose-to-effect per pharmacologic/clinical result; their failure to use the omega-3 index as a validated biomarker is a clear failure in their work, and one that reveals negligence.

Also, supplementation with n3 polyunsaturated fatty acids may increase the need for fat-soluble antioxidants; untoward effects (including inefficacy) may be due to antioxidant depletion—especially in patients already under oxidative stress—rather than due to the n3 supplementation itself.

EPA and DHA. Then the question becomes, well, do you want to use EPA, DHA or a combination of the two? And what this article shows is that DHA is more potent in increasing the Omega-3 Index than is EPA.

In order to summarize and clarify, let's take a look at this excerpt from the article, "A high Omega-3 Index, which reflects a relatively high content of EPA and DHA in membranes of red blood cells, has been associated with lower risk of coronary heart disease and mortality in observational studies. Emerging evidence suggests that DHA may be more potent than EPA in modifying cardiometabolic risk." And they conclude, toward the bottom, "The increase in the Omega-3 Index is significantly greater after supplementation with **high-dose DHA, at 2.7 grams (2,700 mg) per day**, than with a comparable dose of EPA." DHA is more potent than EPA in increasing the Omega-3 Index, and a good amount of research suggests, if not shows, that DHA is more cardioprotective. Now let's go back to the analysis of this article and look at the DHA content of the supplements that were used. Again, you'll see that the doses were at sometimes zero, and other times, quite low: 200, 350 milligrams, 150 milligrams—that's not much at all, 380 milligrams and 375 milligrams. **At no point in time were the majority of these studies that were included in this meta-analysis actually capable of providing a good therapeutic outcome when you look at the DHA content.** You see that throughout most of these studies. The content was too low and, therefore, was not going to be adequate for providing cardioprotection.

Before we leave this page, I will make a few more points, which are tabulated here. The two most common strategies for (un)scientific sabotage of nutritional studies are 1) insufficient dosing and 2) insufficient duration. You can see that I have talked about this with regard to vitamin D studies in an article that you can get online at ICHNFM.org/d. Nutritional interventions, especially fatty acid supplementation, function via changes in *structure and function*—in this case changing cell membranes and gene expression, not—as with drugs, the instantaneous blocking of enzymes and receptors. Therefore, not surprisingly, for fatty acids to exchange in cell membranes and reach a new steady state, a **minimum of five months of treatment is required.**

Furthermore, nothing justifies the constant use of the lowest imaginable dose. If you look at these studies, not only were they underpowered therapeutically, but they used the lowest possible dose that they could get away with and still call it a study. And I think that that's really a disservice, not simply to the entire medical community that's trying to understand this, and not simply to science itself, and not simply to the patients, but it's really just wasting time basically when these articles use subtherapeutic doses of nutrients as if they are searching for the conclusion to show that the nutrients didn't work for whatever the desired outcome might have been. Basically, **everybody gets shortchanged when these articles are underpowered, either in terms of dosing or duration** or other contexts.

Speaking of context, let's take a look at this article from the *Journal of the American Heart Association* published in 2013.⁵ Remember, this article that we're analyzing here from *JAMA Cardiology* was published in early 2018, so they had at least four, if not five years, to take advantage of the research that was published here and certainly not in an obscure journal, this is *Journal of the American Heart Association*. And you'll see, again, what's being discussed here is the Omega-3 Index, which is the sum of EPA and DHA content in red blood cell membranes. This is a biomarker of omega-3 fatty acid status highly correlated with myocardial EPA and DHA content. Basically, what was just stated there is that by looking at this Omega-3 Index, by looking at

Imagine a publication dedicated not to informing but to maintaining selective ignorance

The Omega-3 Index has been reviewed and validated since at least 2007; why was it ignored for a headlining article in *JAMA Cardiology* in 2018?

"The omega-3 index has been validated as a surrogate for myocardial omega-3 FA composition in the human and as such reflects the omega-3 status of the most critical organ. It can be used to both assess baseline omega-3 status and to check for compliance with recommendations to increase omega-3 intake. Altering the omega-3 index is simple, safe and inexpensive and has been shown in randomized trials to reduce risk for CHD death. The widespread clinical implementation of the omega-3 index will allow clinicians to detect omega-3 "insufficiency", to better stratify patients with respect to risk for SCD, and could ultimately contribute to a reduced burden of CHD."

Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res* 2007 Mar

⁵ Flock et al. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *J Am Heart Assoc*. 2013 Nov 19;2(6):e000513 <https://doi.org/10.1161/JAHA.113.000513>

the fatty acids in red blood cell (RBC) cell membranes, you are actually taking basically a virtual biopsy of the heart to see what fatty acids are constituting that heart tissue. They go on to state, "An Omega-3 Index of equal to or greater than 8%," remember what I had said earlier, I recommend 10%, "has been recommended as a cardioprotective level on the basis of associations with reduced risk of primary cardiac arrest, sudden cardiac death, coronary atherosclerosis and acute coronary syndrome. In studies of Americans not taking omega-3 fatty acid supplements, the mean Omega-3 Index values range from 4% to 5%." And, again, we want 10%, which is only achieved through frequent consumption of fatty fish or the use of fatty acid supplements. And, again, this was published in the *Journal of the American Heart Association* in 2013. (Note that the omega-3 index has been validated in publications since before 2007⁶—that is a full 11 years before the publication of this *JAMA Cardiology* article in 2018.) We're using this to critique an article published in 2018. How is it that these authors, publishing in *JAMA Cardiology*, remained selectively ignorant of this very important publication? Let's look at an excerpt from this article. "Participants taking 900 milligrams per day achieved a median Omega-3 Index of 7.6%," so that's a little bit low, "whereas the 1800 milligram per day group achieved a median Omega-3 Index of 9.9," or almost 10%, which is exactly what I had stated previously. Based on this, I think we're justified in stating that 1800 milligrams is the appropriate therapeutic dose to achieve the desired Omega-3 Index, which we want to see at approximately 10%, certainly more than 8%. And, again, we achieve that by a dose of approximately 1800 milligrams per day of EPA and DHA.

Now let's look at which of these studies provided that minimal therapeutic amount. Certainly, this one did not... This one also gets excluded... This one **did not provide any DHA at all**, so it's, of course, excluded. The following study was also inadequately dosed. Same with the following, the following and this one. Again, we're left with only three articles out of the 10 that reasonably represent what we might consider to be an appropriate intervention or, as we might say, the current state of the art.

The question that I started to ask, when I was looking at this article, is **how on earth can a meta-analysis on omega-3 fatty acids and cardiovascular disease get published in a cardiology specialty journal in 2018 without any mention whatsoever of the Omega-3 Index?** My conclusion to my own rhetorical question is that **this is the intentional creation and propagation of nutritional ignorance, not simply among the population, but specifically among the population of medical physicians who do not receive nutritional training in their years of medical school and now are simply perpetuating their ignorance by giving them an article, like this one published in JAMA Cardiology, which misrepresents the science.**

3. **Error in use of unnatural/semisynthetic form of fish oil:** In addition to low dosing, some people would probably argue that because most of these studies used an *unnatural* or *semisynthetic* form of fatty acid supplementation that that's also a disadvantage to the majority of the studies that were included in this meta-analysis. Nine of the 10 studies used in this meta-analysis used synthetic or semisynthetic, the ester form, of omega-3 fatty acids. This is in contrast to the natural, and arguably easier to digest, triglyceride form. And you can see that that was stated in this excerpt, "Combinations of polyunsaturated fatty acid ethyl esters of EPA and DHA were used in all but one trial," and that one trial used EPA *without any DHA*, so it was obviously hindered in its ability to produce the desired outcome.

The daily doses, just to review again, the daily doses of EPA varied from 226 milligrams to 1800 milligrams per day and the DHA content varied from zero to 1700 milligrams per day. Well, obviously, zero would be subtherapeutically dosed because that is basically **providing zero content of what is now considered to be the more important of the two fatty acids between EPA and DHA**. Again, these days, many would argue that DHA is at least as important as EPA, so **the inclusion of studies that have zero or insufficient content of the active component is pretty much ridiculous**. Again, no meta-analysis, and probably no primary research article, that under-dosed a medication would get published in a big, mainstream, headlining journal. The editors would reject it and they would say, "*Well, of course, your study didn't work out because you only provided 30% of the dose.*" But here, when they do that with nutrition, they publish it, it gets 100,000 reads in two weeks, and it makes the headlines in probably every newspaper.

4. **Error in conclusions at odds with data:** Critique number four that I have of this article is stated conclusion at odds with the data. They say that they found no significant associations when, in fact, the associations that they

⁶ Harris WS. Omega-3 fatty acids and cardiovascular disease: a case for omega-3 index as a new risk factor. *Pharmacol Res.* 2007 Mar;55(3):217-23

did find were all favorable toward fish oil. You can see here in this table, they are showing the information that either favors treatment or favors control. If we are on this side of the line (see video for graphic presentation), then that favors treatment, over here favors no treatment. The data that supports the use of fish oil is basically summarized by these images here. You can see the bigger boxes represent more data and more patients. The smaller boxes indicate a smaller amount of information. If you just look at the graph, you will see that most of the data favors treatment. The boxes are bigger and we have more boxes on this side. Six out of 10 of the studies actually favor fish oil supplementation and also; not only do we have more studies, but we also have larger populations of subjects represented by that data. Not only do we see more studies supporting this view, but we also see larger groups of patients benefiting than not benefiting from fish oil supplementation. This was figure #1 from the article; figure #2 showed the same trend (see video or article).

Let's take a look at another figure here. We're going to look at figure #3. Again, you see most of the outcomes favor treatment with fish oil. You see more boxes on this side than you do on this side. And, again, here, from their figure #4, we see more data points and larger data points on this side. All of these favor fish oil supplementation basically. "Associations With Omega-3 Fatty Acids, Fatal and Nonfatal Vascular Events by Trial Design," again, all of these, or what appears to be virtually all of these, favor treatment with fish oil supplementation, yet the authors publish the conclusion that omega-3 fatty acids were not beneficial for the prevention of cardiovascular disease and death.

5. Pro-pharma conflicts of interest among authors, publication, and supporting organizations: Critique number five that I have for this article is simply that most of the authors had affiliations with medical schools, which are brutally pro-pharma and anti-nutrition and that several of the authors were paid directly by drug companies that sell drugs of interest to the prevention of cardiovascular disease. Nearly all medical schools and organizations are rabidly pro-pharm and pro-chem, lovingly accepting money from drug and chemical companies and promoting faculty that are pro-drug and anti-nutrition, and I suspect that that's what we're looking at here in their author affiliations and conflicts of interest.

Conclusion and summary of major points of critique: Finally, to summarize my critique of this article, problems with this publication: ❶ unjustified selective exclusion of data, ❷ inclusion of studies that employed subtherapeutic or non-therapeutic dosing. This article really took under-dosing to the extreme and completely ignored a foundationally important advance in cardiology and biomedical science and that is the Omega-3 Index. ❸ Nine of the 10 studies used in this meta-analysis used a synthetic ester form of omega-3 fatty acids. This is in contrast to what many would prefer, the natural, easier to digest triglyceride form. ❹ Their stated conclusion that omega-3 fatty acids are not efficacious for the prevention of cardiovascular disease and death is at odds with the data that they presented, and ❺ I think the pro-pharma conflicts of interest among the authors and the publishing organization are also worthy of comment.

Thank you very much for your attention during this brief analysis of this article, and I look forward to sharing more nutrition information with you in the very near future. ✨

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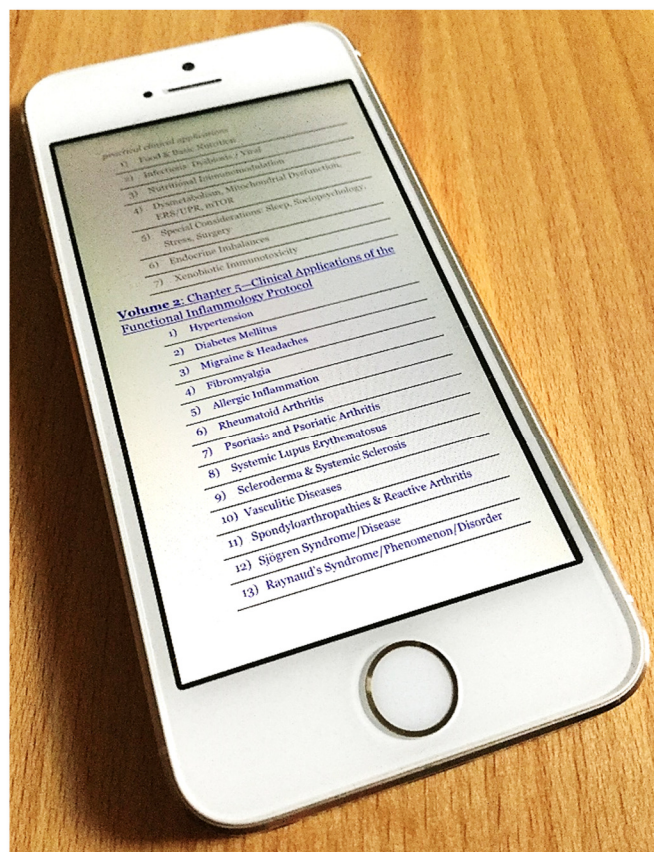
About the author: Dr Vasquez holds three doctoral degrees and has completed hundreds of hours of post-graduate and continuing education in subjects including Obstetrics, Pediatrics, Basic and Advanced Disaster Life Support, Nutrition and Functional Medicine; while in the final year of medical school, Dr Vasquez completed a Pre-Doctoral Research Fellowship in Complementary and Alternative Medicine Research hosted by the US National Institutes of Health (NIH). Dr Vasquez is the author of many textbooks, including the 1200-page Inflammation Mastery 4th Edition (2016) also published as a two-volume set titled Textbook of Clinical Nutrition and Functional Medicine. "DrV" has also written approximately 100 letters and articles for professional magazines and medical journals such as *TheLancet.com*, *British Medical Journal* (BMJ), *Annals of Pharmacotherapy*, *Nutritional Perspectives*, *Journal of Manipulative and Physiological Therapeutics* (JMPT), *Journal of the American Medical Association* (JAMA), *Original Internist*, *Integrative Medicine*, *Holistic Primary Care*, *Alternative Therapies in Health and Medicine*, *Journal of the American*

Osteopathic Association (JAOA), *Dynamic Chiropractic*, *Journal of Clinical Endocrinology and Metabolism*, *Current Asthma and Allergy Reports*, *Complementary Therapies in Clinical Practice*, *Nature Reviews Rheumatology*, *Annals of the New York Academy of Sciences*, and *Arthritis & Rheumatism*, the Official Journal of the American College of Rheumatology. Dr Vasquez lectures internationally to healthcare professionals and has a consulting practice and service for doctors and patients. Having served on the Review Boards for *Journal of Pain Research*, *Autoimmune Diseases*, *PLOS One*, *Alternative Therapies in Health and Medicine*, *Neuropeptides*, *International Journal of Clinical Medicine*, *Journal of Inflammation Research* (all PubMed/Medline indexed), *Integrated Blood Pressure Control*, *Journal of Biological Physics and Chemistry*, and *Journal of Naturopathic Medicine* and as the founding Editor of *Naturopathy Digest*, Dr Vasquez is currently the Editor of *International Journal of Human Nutrition and Functional Medicine* and the Director for International Conference on Human Nutrition and Functional Medicine. Dr Vasquez has also served as a consultant researcher and lecturer for Biotics Research Corporation.

Contextualizing resource—same information in different formats and contexts:

- *Inflammation Mastery, 4th Edition* <https://www.amazon.com/dp/B01KMZZLAQ/> and
- *Textbook of Clinical Nutrition and Functional Medicine, vol. 1: Essential Knowledge for Safe Action and Effective Treatment* <https://www.amazon.com/dp/B01JDIOHR6/>

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Introductory videos:

- Video introduction to books: <http://www.ichnfm.org/im4>
- Current video: <http://www.ichnfm.org/jama2018n3>
- Conference presentation—introducing the clinical protocol: <http://www.ichnfm.org/video-funct-inflam-1>

