

# What to Tell Your Patients: A Critical Review of the *JAMA Cardiology* Meta-Analysis “Associations of Omega-3 Fatty Acid Supplement use with Cardiovascular Disease Risks”

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## ABSTRACT

Authors of a meta-analysis recently published in *JAMA Cardiology* concluded that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events. This critical review examines participant profile, intervention dosage, bioavailability of intervention, and duration of therapy for the cited trials and determines that the conclusion of the meta-analysis is tentative at best.


**Keywords:** DHA; EPA; omega-3 fatty acids; cardiovascular health; heart disease

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## INTRODUCTION

Authors of a recent meta-analysis published in *JAMA Cardiology* concluded that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events.<sup>1</sup> A meta-analysis is only as meaningful as the trials from which it aggregates data. Factors such as participant profile, intervention dose, bio-availability of intervention, and duration of therapy potentially affect treatment efficacy. The present critical review examines each of these factors in the context of the *JAMA Cardiology* article to help clinicians understand the article’s limitations in order to better answer patients’ questions on the topic.

The article reviewed here is entitled “Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: meta-analysis of 10 trials involving 77,917 individuals.” It was published in *JAMA Cardiology* in early 2018. It is recommended that readers obtain the original article for access to tables and figures referenced here. In addition, please watch AV’s video critique ([ichnfm.org/jama2018n3](http://ichnfm.org/jama2018n3)) on which this article is based.

## PARTICIPANT PROFILE

The mean ages of participants in each of the cited studies ranged from 59 to 74 years old (*see* the table “Characteristics of Included Trials” in the original article). Some of the studies included patients who already had metabolic syndrome and cardiovascular disease. This means the study populations were older and included people who likely had a very different risk profile from patients who begin polyunsaturated fatty acid (PUFA) supplementation early in a disease process. At least one observational study that followed patients who were hospitalized for acute myocardial infarction showed that early use of  $\omega$ -3 PUFAs was associated with a reduction in 1-year all-cause mortality and recurrent infarction.<sup>2</sup> It’s important, therefore, to understand the profile of participants enrolled in studies, because it affects the generalizations that can be made about an intervention. Furthermore, if a study population is largely unhealthy, it may raise

questions about whether intervention dosing is at therapeutic levels.

## INTERVENTION DOSING

The authors of the meta-analysis state, “All eligible trials required use of supplements, but no minimum daily dose of EPA or DHA was specified.” The studies included used widely different doses of the intervention, ranging from 226 mg/d eicosapentaenoic acid (EPA) plus 150 mg/d docosahexaenoic acid (DHA) to 1150 mg/d EPA plus 800 mg/d DHA. In addition, one study used only EPA (1800 mg/d) and no DHA (*see* “DHA and EPA” section below for more commentary on this). The variability in dosage alone should have been seen as a limitation in the meta-analysis. Another trial<sup>3</sup> (not included in the meta-analysis) showed that a *minimum* of 1 g/d of  $\omega$ -3 PUFAs is required in patients after infarction for cardioprotective benefit. In fact, the American Heart Association issued a science advisory in 2017<sup>4</sup> which concluded that  $\omega$ -3 PUFA supplementation is potentially useful for patients with prevalent coronary heart disease, but that supplement doses of even approximately 1000 mg/d are “generally too low.” Using this recommendation as a guideline, 7 of 10 studies cited in this meta-analysis used subtherapeutic dosing.

Another concern regarding dosing in the studies included in this meta-analysis is that the studies did not follow the recommendations put forward in the Omega-3 Index (O3I). The O3I is a validated biomarker of  $\omega$ -3 fatty acid tissue levels. It is calculated as the proportion of EPA and DHA in red blood cell membranes and is inversely associated with the risk of coronary heart disease and coronary mortality.<sup>5</sup> An O3I greater than or equal to 8% has been recommended on the basis of its association with reduced risk of all-cause mortality, cardiac death, and sudden death in post-myocardial infarction patients. A randomized controlled trial that looked at the dose-response relationship of  $\omega$ -3 PUFA supplementation found that no participant assigned to a dose less than or equal to 600 mg/d attained an O3I of 8%. Participants taking 900 mg/d achieved a

median O3I of 7.6%, whereas the 1800 mg/d group achieved a median O3I of 9.9%.<sup>6</sup> On the basis of these findings, the authors concluded that an average *healthy* adult with a low O3I (4.3%) would require *at least* 1 g/d of both EPA and DHA for 5 months to attain a level of 8%. Only 3 of the 10 studies cited in the meta-analysis used appropriate dosing to potentially achieve 8% on the O3I, but none of these three used at least 1 g/d of both EPA and DHA, and one study used no DHA at all. Remember also that many participants in the cited studies were not healthy; therefore, arguably even higher doses would have been needed to reach therapeutic levels.

## DHA AND EPA

Emerging evidence suggests that DHA may be a more potent modifier of cardiometabolic risk than EPA. This difference is reflected in O3I levels. One study found that the increase in O3I levels was significantly greater after supplementation with 2.7 g/d DHA than with a comparable dose of EPA.<sup>7</sup> Seven of the ten studies cited in the *JAMA Cardiology* meta-analysis used doses of DHA that were less than or equal to 500 mg/d, with one of these studies using no DHA at all. The DHA content of the interventions in the included studies was likely insufficient to be associated with cardioprotection.

## BIOAVAILABILITY OF INTERVENTION

Nine of the ten studies cited in this meta-analysis used synthetic or semisynthetic (ethyl ester) forms of  $\omega$ -3 fatty acids instead of the more digestible triglyceride form. The 10th trial used only EPA without DHA. Evidence suggests that plasma levels of  $\omega$ -3 PUFAs are more significant predictors of cardiovascular events than the amount consumed.<sup>8,9</sup> The lack of efficacy observed in this meta-analysis could be explained in part by the possibility that the forms of intervention used had poor bioavailability.

## DURATION OF TRIALS

Nutritional interventions generally have their effect over time via changes in structure and function. In contrast, pharmaceutical agents often work by the almost instantaneous blocking of enzymes and receptors. Obtaining meaningful dietary supplement and health relationship data, particularly for atherosclerotic cardiovascular disease outcomes, could take many years. It is possible that some trials included in the meta-analysis were too short to show an effect.

### **Box 1: *JAMA Cardiology* meta-analysis “Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks”: quick reference points to share with patients**

This paper was a meta-analysis, which is the term for a statistical procedure that combines data from multiple studies to try to find similar effects. The authors of this meta-analysis concluded that there is no evidence to support using fish oil supplementation for protection with regard to cardiovascular disease risk. However, there were enough issues with the majority of the studies included in the meta-analysis to cast doubt on the authors’ conclusions:

- Many study participants already had cardiovascular disease, which is not equivalent to looking at the preventative effects of fish oil supplementation on cardiovascular disease or its ability to be protective if used soon after a heart attack.
- The dosages of fish oil supplements used in the different studies varied tremendously, with most of them too low to reasonably expect positive results.
- Most of the studies used fish oil supplements that were synthetic or semisynthetic and likely not as absorbable as natural forms.
- Some of the studies were too short in duration to expect to see a positive outcome.

## CONCLUSION

Please watch AV’s video presentation, which is available at [ichnfm.org/jama2018n3](http://ichnfm.org/jama2018n3), for a step-by-step interpretation of the results presented in the original *JAMA Cardiology* article. **Quick reference points to share with patients** are given in Box 1.

## IMPLICATIONS FOR CLINICIANS

On the basis of an examination of the participant profile, intervention dosage, bioavailability of intervention, and duration of therapy, the studies cited by the *JAMA Cardiology* meta-analysis are sufficiently flawed for the conclusion that omega-3 fatty acids have no significant association with fatal or nonfatal coronary heart disease or any major vascular events to be interpreted with caution. The authors themselves state that their 95% confidence intervals cannot exclude the possibilities of an association between  $\omega$ -3 PUFA supplementation and a 7% reduction in the risk of major cardiovascular events and a 10% reduction in the risk of ischemic events. To provide better answers, future studies could recruit participants with a low O3I and treat them to within a predetermined therapeutic range. Until the results of better-designed trials are available, and given the low risks associated with  $\omega$ -3 PUFA supplementation, clinicians are advised to, at the very least, continue with the recommendations of the American Heart Association<sup>4</sup> and give patients with left ventricular dysfunction and a high arrhythmic risk who are in their first year after infarct a minimum of 1 g/d  $\omega$ -3 PUFA supplementation.

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## SUMMARY OF KEY POINTS

**Participant profile:** In general, the study populations were older and included people who already had cardiovascular disease. This is a very different risk profile from patients who begin PUFA supplementation early in a disease process.

**Intervention dosage:** Doses of  $\omega$ -3 PUFAs varied widely among the trials. At least 7 of 10 studies used subtherapeutic dosing. One trial used only EPA and no DHA. Emerging evidence suggests that DHA may actually be more cardioprotective than EPA.

**Bioavailability of intervention:** Nine of ten studies used synthetic or semisynthetic (ethyl ester) forms of  $\omega$ -3 fatty acid supplements, which are potentially less bioavailable than the natural triglyceride form.

**Trial duration:** Studies of nutritional interventions generally take longer than drug trials to yield meaningful data. Many trials included in the meta-analysis were likely of too short a duration to show a treatment effect.

Ongoing studies continue to reinforce that supplementation with  $\omega$ -3 PUFAs carries low risk. Given this low-risk profile, along with the recommendations of the American Heart Association, clinicians are advised to supplement postinfarction patients who have left ventricular dysfunction and a high arrhythmic risk with *at least* 1 g/d  $\omega$ -3 PUFAs.

## COMPETING INTERESTS

The authors declare they have no competing interests.

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# 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 4<sup>th</sup> 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](http://ichnfm.org/jama2018n3), and the transcript in PDF format—which is considered the final and citable version—is archived at [academia.edu/35935996](http://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.”<sup>1</sup> 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-

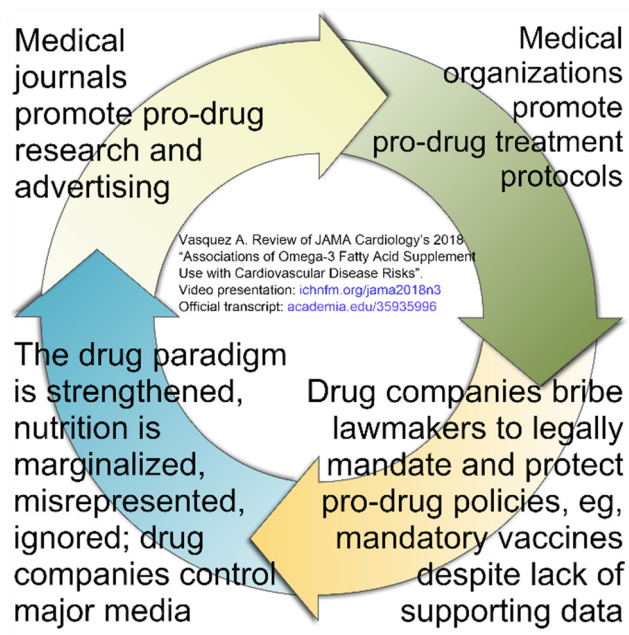
<sup>1</sup> Aung et al. Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks. *JAMA Cardiol* 2018 Jan 10.1001/jamacardio.2017.5205

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.<sup>2</sup>) 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.<sup>3</sup> 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

<sup>2</sup> 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](https://doi.org/10.1371/journal.pmed.0020138)

<sup>3</sup> 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-eficacious 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.<sup>4</sup> 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 &amp; Corrections</p> <p>"Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks" JAMA Cardiology January 31, 2018</p>	<p><b>Errors in this publication</b></p> <p><b>2. ERROR by inclusion of studies that employed nontherapeutic dosing:</b> "... no minimum daily dose of EPA or DHA was specified..."</p> <ul style="list-style-type: none"> <li>▶ Like I stated previously with regard to vitamin D, "subphysiologic dosing is subtherapeutic." (<i>Lancet.com</i> 2005 May, archived at <a href="http://ichnfm.org/d">ichnfm.org/d</a>)</li> <li>▶ 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 <b>everyone knows that dose-response relationships are of huge importance</b>. Therefore, <b>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.</b></li> </ul> <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 <b>no minimum daily dose of EPA or DHA was specified</b>. The prescrip-</p> </div>
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<sup>4</sup> 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](http://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.<sup>5</sup> 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

<sup>5</sup> 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 2007<sup>6</sup>—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

<sup>6</sup> 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. ✂

**Citation:** Vasquez A. Review of *JAMA Cardiology's* 2018 "Associations of Omega-3 Fatty Acid Supplement Use with Cardiovascular Disease Risks." Video presentation ([ichnfm.org/jama2018n3](http://ichnfm.org/jama2018n3)) and official PDF transcript ([academia.edu/35935996](http://academia.edu/35935996)) 2018 Jan

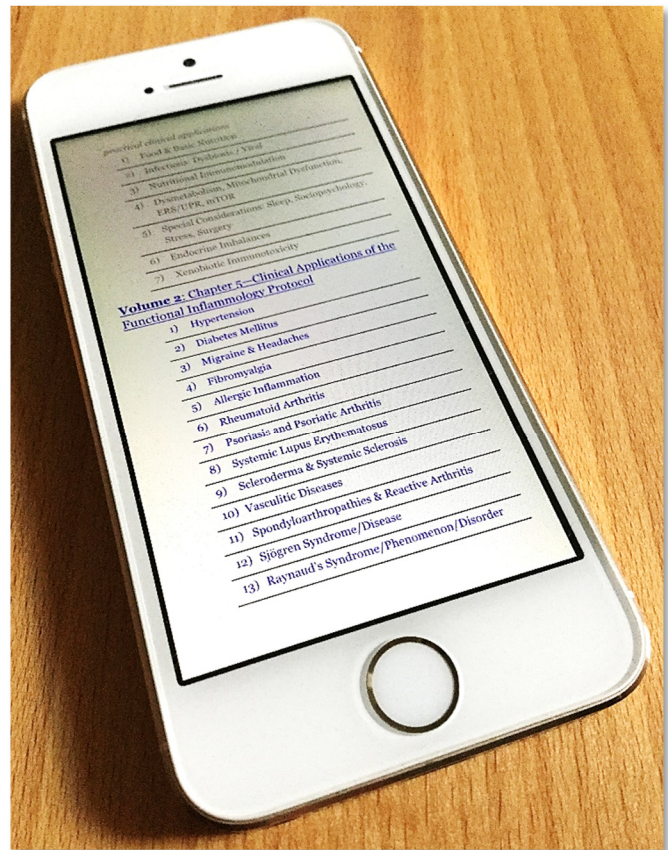
**About the author:** Dr Vasquez holds three doctoral degrees and has completed hundreds of hours of post-graduate and continuing education in subjects including Obstetrics, Pediatrics, Basic and Advanced Disaster Life Support, Nutrition and Functional Medicine; while in the final year of medical school, 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 4<sup>th</sup> 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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- 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>





Please review the Supplemental Files folder to review documents not compiled in the PDF.

**Letter re: ASCEND Study: N Engl J Med 2018 Aug 26  
doi:10.1056/NEJMoa1804989**

Journal:	<i>New England Journal of Medicine</i>
Manuscript ID	Draft
Article Type:	Letter about NEJM Article
Date Submitted by the Author:	n/a
Complete List of Authors:	Vasquez, Alex; ICHNFM
Abstract:	

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ASCEND showed no advantage of 1,000 mg/d marine n3 fatty acids against equally-dosed naturally occurring olive oil. Olive oil apparently reduces cardiovascular and total mortality<sup>1</sup>, while oleic acid shows direct vascular antiinflammatory, atheroprotective, and antidiabetic benefits.<sup>2</sup> A six-week trial among overweight subjects reported that olive oil 2 g/d was more effective than equidosed fish oil for reducing fasting glucose, HgA1c, hsCRP, and IL6.<sup>3</sup> A six-month trial among rheumatic patients showed that 6 g/d of olive oil provided analgesic and antiinflammatory benefits, leading the authors to conclude, "Olive oil can no longer confidently be used as a placebo control."<sup>4</sup> Using olive oil as a comparator against other antiinflammatory treatments diminishes the therapeutic differential and apparent benefit for both substances; this results in a type-2 error and underappreciation of therapeutics' effectiveness. 10% of ASCEND subjects were taking n3 supplementation at baseline, with corresponding omega-3 indexes of 6.6% and 7.1%, remarkably higher than the average 4% typical of Western societies.<sup>5</sup> Pre-treatment plus high baseline status would reduce the clinical response to intervention with n3 and olive oil supplementation.

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On Mon, Dec 3, 2018 at 10:48 PM NEJM Letter wrote:

Dear Dr. Vasquez,

I am sorry that we will not be able to publish your recent letter to the editor regarding the Armitage article of 18-Oct-2018. The space available for correspondence is very limited, and we must use our judgment to present a representative selection of the material received. Many worthwhile communications must be declined for lack of space. Thank you for your interest in the Journal.

Sincerely,

-- G. -- M.D.

Deputy Editor

New England Journal of Medicine

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nejm.org

From: Dr Alex (Kennerly) Vasquez ICHNFM

Date: Wed, Dec 12, 2018 at 1:37 PM

Subject: Re: New England Journal of Medicine 18-12067

To: nejm

Not surprising, considering that Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies, per *PLoS Med* 2(5): e138.

<https://doi.org/10.1371/journal.pmed.0020138>

Problems with your published article include the following:

1. Under-dosed fish oil: described below

2. Inappropriate placebo: The ASCEND study used an inappropriate placebo against underdosed fish oil, ultimately to pave the way for greater acceptance of the late-year launch of "purified prescription fish oil"...how convenient: AHA: Prescription Fish Oil Wins for CV Prevention, November 10, 2018 <https://www.medpagetoday.com/meetingcoverage/aha/76252>

3. Bad research in support of a new pharmaceutical drug launch: per above

4. Supervision of the trial authors by the drug company paying the authors: what a joke of an article

5. Complete failure to disclose conflicts of interest among the authors in the published paper.

6. Plenty of space: NEJM clearly has 250 words of space to publish these concerns, so only an imbecile would think that the journal "does not have space" to publish my critique. The original article had approximately 6,970 words (per computerized count) so that 250 words in a letter such as mine is less than 4% of the original article.

To see an accurate review of your garbage research, please see my video review: <https://vimeo.com/287650812>

Sincerely,

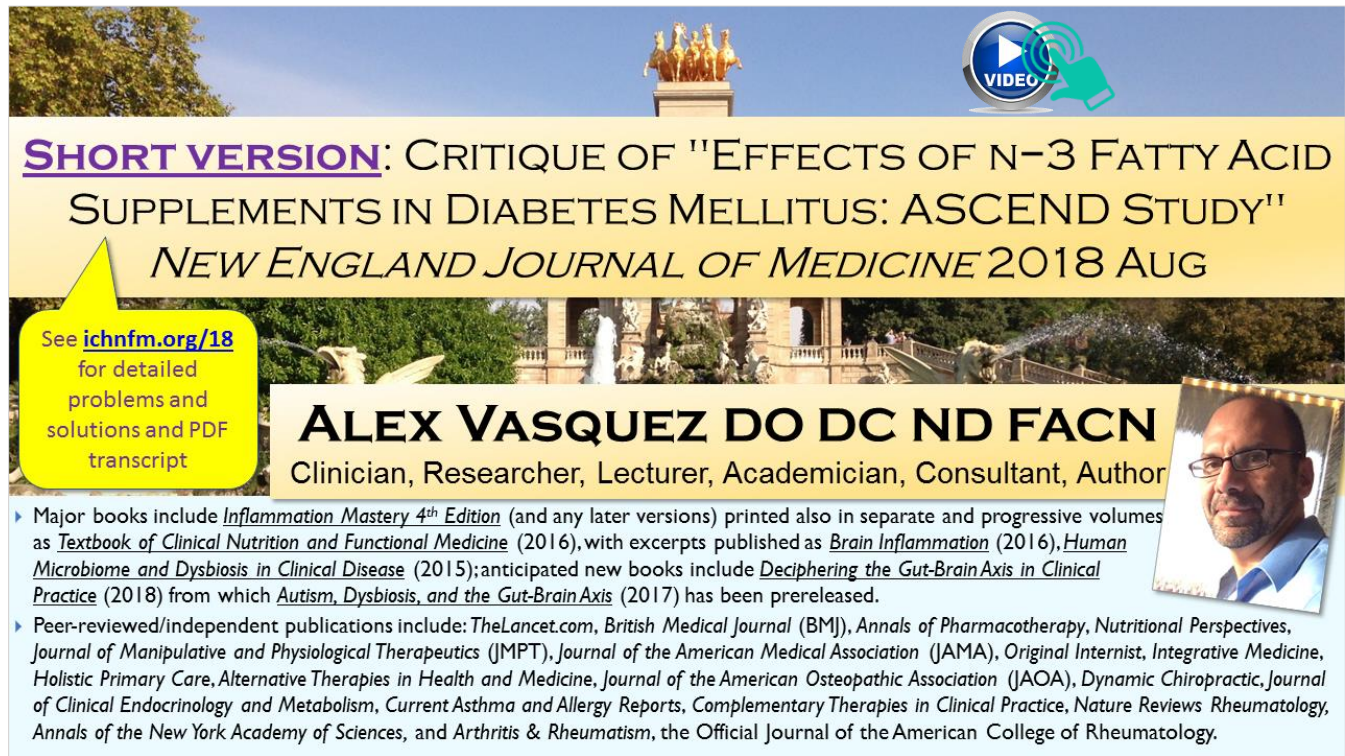
Dr Alex (Kennerly) Vasquez

Confidential: Destroy when review is complete.



# Brief Critique of "Effects of n3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study"

## New England Journal of Medicine 2018 Aug



**SHORT VERSION:** CRITIQUE OF "EFFECTS OF N-3 FATTY ACID SUPPLEMENTS IN DIABETES MELLITUS: ASCEND STUDY"  
NEW ENGLAND JOURNAL OF MEDICINE 2018 AUG

See [ichnfm.org/18](http://ichnfm.org/18) for detailed problems and solutions and PDF transcript

**ALEX VASQUEZ DO DC ND FACN**  
Clinician, Researcher, Lecturer, Academician, Consultant, Author

- 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* (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.


The video of this presentation is archived at [ichnfm.org/18](http://ichnfm.org/18), and the transcript in PDF format—which is considered the final and citable version—is archived at [academia.edu/37326521](http://academia.edu/37326521); 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 **September 2, 2018**.

**Introduction:** Hello everyone. This is Dr. Alex Vasquez with the short version of my “Critique of the Effects of Omega 3 Fatty Acids Supplements in Diabetes” recently published as the Ascend Study in the *New England Journal of Medicine*, 2018 August. If you'd like to see the longer and more detailed version of this review, please see [ichnfm.org/18](http://ichnfm.org/18) for my videos from 2018.

**This was *not* a placebo-controlled study:** This is a randomized and *supposedly* “placebo-controlled” trial of 15,000 subjects. The intervention included either omega-3 fatty acids or olive oil—so this was *not a placebo-controlled study*. This was a *comparison* of relatively low-dose EPA and DHA against low-dose olive oil—so again, this is *not* a placebo-controlled study.

This study used *two* active interventions. One was fish oil and the other was olive oil, both of which are notably anti-inflammatory and cardioprotective. As such, the conclusion from this study that fish oil does not benefit diabetic patients is completely invalid. Furthermore, neither of the two active treatments were independently tested for their components and both of the treatments were provided by a drug company that has a financial interest in the failure of these treatments.

The drug company, Mylan, specifically paid 19 of the authors, oversaw the study design and supervised its paid consultants at key meetings, provided the treatment and the active comparator, neither of which again were independently tested, and also makes the main competing drug in this category of cardioprotection, in this case the statin drug, simvastatin.

DR VASQUEZ'S RESEARCH REVIEW	<u><i>Olive oil is not a placebo but is clinically active in humans, starting with low doses: biological mechanisms</i></u>	ALEX VASQUEZ DO ND DC FACN
Today's main article being reviewed	▶ <b>Mechanisms of action and biological plausibility:</b> Squalene is also worthy of consideration	
Problems with this publication	▶ <b>Oleic acid:</b> May be described as a “conditionally essential nutrient”; component of cell membranes and thus modifies inflammatory mediator production and transmembrane signaling; directly cardiovascular-protective; “interferes directly with the inflammatory response that characterizes early atherogenesis... decreases the expression of several endothelial leukocyte adhesion molecules, among which vascular cell adhesion molecule-1, involved in the selective monocyte recruitment in the arterial intima. Oleic acid also determines a parallel reduction in messenger RNA for this molecule, interfering with the activation of the most important transcription factor controlling endothelial activation, nuclear factor-kappa B. ... oleic acid may contribute to the prevention of atherosclerosis also through a modulation of gene expression for endothelial leukocyte adhesion molecules” per Massaro et al, <i>Cardiologia</i> 1999 Jun	
Noting the pattern of bogus research	▶ <b>Phytochemicals/polyphenols:</b> Ibuprofen-like antiinflammatory activity; notably potent antioxidant and antiinflammatory activity; “antidiabetic effect” per reduction of glycosylated proteins such as HgbA1c and normalization of fasting glucose even at low doses; inhibition of HER2 (erbB-2)-induced malignant transformation (breast cancer); neuroprotective; modulation of gut microbiota is notably relevant for T2DM.	Doctor of Osteopathic Medicine (DO—UNTHSC, USA)
What can be done	For additional context, clinical applications, and disease-specific as well as general protocols, see <b><i>Inflammation Mastery 4<sup>th</sup> Edition</i></b> <a href="http://ichnfm.org/im4">ichnfm.org/im4</a> and/or the two-volume set <b><i>Textbook of Human Nutrition and Functional Medicine</i></b> from <a href="http://amazon.com/author/alexvasquez">amazon.com/author/alexvasquez</a>	Doctor of Naturopathic Medicine (ND—Bastyr University, USA)
What clinicians should do		Doctor of Chiropractic (DC—Western States, USA)
Critique of "Effects of n-3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" New England Journal of Medicine 2018 Aug		Overseas Fellow, Royal Society of Medicine
		Fellow, American College of Nutrition
		Author of <i>Inflammation Mastery</i> , <a href="http://ichnfm.org/im4">ICHNFM.ORG/im4</a>

This trial is invalidated by the use of an active treatment erroneously described as “placebo.” It may be randomized, but it is *not* placebo-controlled.

They started this study in 2005 and at that time they already knew that olive oil was cardioprotective. In fact, that had been published in *The New England Journal of Medicine* in 2003, two years prior to the start of this study. Their claim that they used olive oil as a placebo is completely absurd because olive oil is well known to have anti-inflammatory and cardioprotective benefits, and more specifically, olive oil is known to be one of the most health-promoting and heart-protecting dietary components available.

The cardioprotective benefits of olive oil have been suggested in the research since the 1950s, were more established by 1986 in a key study, and have since been validated clinically and mechanistically.

In my more than 20 years of looking at biomedical research I have never seen a drug company so well entrenched within a study design including supervising key meetings and paying 19 of the authors. In the text of the article the authors describe themselves as “independent investigators” despite the fact that 19 of them received payment from various drug companies intimately involved with the study.

Furthermore, again, the drug company provided both the active treatment and its comparator. Authors were paid by the drug companies, but **these conflicts of interest were not published in the article**, products were not independently tested. The Omega-3 index was tested in 152 subjects; this is less than 1% of the study population, and I found that to be rather weak.

I also noted that their baseline Omega-3 index was abnormally high and their response to the Omega-3 supplementation was also abnormally high considering that they used only one-half of the typically effective dose.

Now let's take a quick look at some examples from the disclosure forms. Again, these were not printed in the article, but they are, of course, highly relevant considering that 19 of the authors were paid by drug companies including Bayer on four different occasions, also Solvay Pharmaceuticals, Abbott Pharmaceuticals and Mylan Pharmaceuticals.

You'll see that this pattern was recurrent among 19 of the authors of this study, and perhaps even more impressive is the fact that this was not published in the article. One has to go to *The New England Journal of Medicine* website to find this documentation.

What can be done about this is that we all have to become better critical thinkers and careful readers so that we can spot these gross errors in biomedical research publications.

What clinicians should do is to continue using fish oil supplements generally at a dose of 1900 milligrams per day if the goal is to optimize the Omega-3 Index to approximately 10%.

Thank you very much for looking at this brief presentation. If you'd like to see the full version, please go to [ichnfm.org/18](http://ichnfm.org/18). Those are the videos I've produced in 2018, and what you'll see there is the complete video as well as a pdf transcript. ☒

**Citation:** Vasquez A. Critique of "Effects of n3 Fatty Acid Supplements in Diabetes Mellitus: ASCEND Study" New England Journal of Medicine 2018 Aug: Video presentation ([ichnfm.org/18](http://ichnfm.org/18)) and official transcript ([academia.edu/37326521](http://academia.edu/37326521)) Date of this revision: September 2, 2018

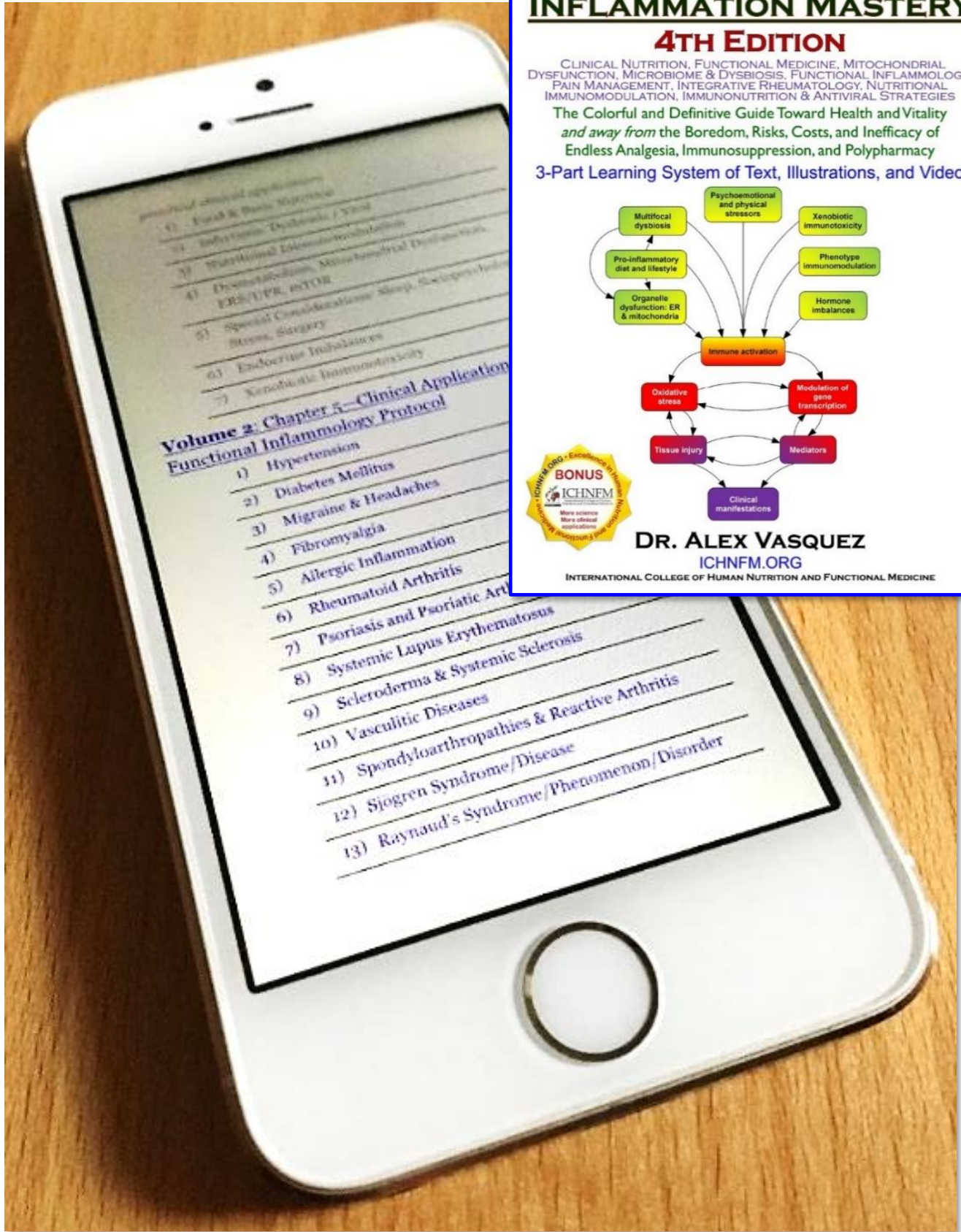
**About the author:** Dr Vasquez holds three doctoral degrees and has completed hundreds of hours of post-graduate and continuing education in subjects including Obstetrics, Pediatrics, Basic and Advanced Disaster Life Support, Nutrition and Functional Medicine; while in the final year of medical school, 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, 4<sup>th</sup> Edition](#). (2016) also published (by popular student request) 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/B01KMZZLQO/) <https://www.amazon.com/dp/B01KMZZLQO/> and
- [Textbook of Clinical Nutrition and Functional Medicine, vol. 1: Essential Knowledge for Safe Action and Effective Treatment](https://www.amazon.com/dp/B01JDIOHR6/) <https://www.amazon.com/dp/B01JDIOHR6/>



See video at <http://www.ichnfm.org/18>



**Introductory videos:**

- Video introduction to books: <http://www.ichnfm.org/im4> and other videos: <http://www.ichnfm.org/18>
- Conference presentation—introducing the clinical protocol: <http://www.ichnfm.org/video-funct-inflam-1>

### Persistent inadequacies in nutrition education/training among physicians

**Introduction:** Despite the acknowledged importance of diet in the prevention of obesity, diabetes, hypertension and other components of cardiometabolic syndrome/disease, physicians are consistently and systematically untrained in nutrition. A few exemplary citations are summarized per the following:

- What do resident physicians know about nutrition? (J Am Coll Nutr 2008 Apr<sup>29</sup>): "OBJECTIVE: Despite the increased emphasis on obesity and diet-related diseases, nutrition education remains lacking in many internal medicine training programs. We evaluated the attitudes, self-perceived proficiency, and knowledge related to clinical nutrition among a cohort of internal medicine interns. METHODS: Nutrition attitudes and self-perceived proficiency were measured using previously validated questionnaires. Knowledge was assessed with a multiple-choice quiz. ... RESULTS: Of the 114 participants, 61 (54%) completed the survey. Although 77% agreed that nutrition assessment should be included in routine primary care visits, and 94% agreed that it was their obligation to discuss nutrition with patients, only 14% felt physicians were adequately trained to provide nutrition counseling. ... CONCLUSIONS: Internal medicine interns' perceive nutrition counseling as a priority, but lack the confidence and knowledge to effectively provide adequate nutrition education." These are impressive results showing that internal medicine doctors—specialists who commonly deal with diabetes, hypertension, obesity, and metabolic syndrome—do not have competence in nutrition, even by weak and basic standards.
- Relevance of clinical nutrition education and role models to the practice of medicine (Eur J Clin Nutr. 1999 May<sup>30</sup>): "Yet, despite the prevalence of nutritional disorders in clinical medicine and increasing scientific evidence on the significance of dietary modification to disease prevention, present day practitioners of medicine are typically untrained in the relationship of diet to health and disease."
- How much do gastroenterology fellows know about nutrition? (J Clin Gastroenterol. 2009 Jul<sup>31</sup>): "The mean total test score was 50.04%. ...CONCLUSIONS: Gastroenterology fellows think their knowledge of nutrition is suboptimal; objective evaluation of nutrition knowledge in this cohort confirmed this belief. A formal component of nutrition education could be developed in the context of GI fellowship education and continuing medical education as necessary."

**In sum:** The data consistently demonstrate that healthcare providers at the doctorate level are untrained in nutrition when assessed by rather simple standards; their knowledge of functional nutrition at the level of clinical intervention in the treatment of serious disease would reasonably be expected to be approximately zero. Thus, given that doctors are trained neither in musculoskeletal management (despite the fact that all patients have musculoskeletal systems and that related disorders represent no less than 20% of general practice) nor nutrition (despite the fact that all patients eat food and that such dietary habits (and/or the use of nutritional interventions) impact nearly all known diseases in the known universe), one might wonder as to the cause and perpetuation of this *systematically imposed ignorance* on such topics of major importance. Consistent faults in medical education are not accidental.

#### Dumbing Us Down: The Hidden Curriculum of Educational Systems

"Look again at the seven lessons of school teaching: confusion, class position, indifference, emotional and intellectual dependency, conditional self-esteem, and surveillance. All of these lessons are prime training for permanent underclasses, people deprived forever of finding the center of their own special genius."

Such a curriculum produces physical, moral, and intellectual paralysis, and no curriculum of content will be sufficient to reverse its hideous effects. ... Schools teach exactly what they are intended to teach and they do it well."

Gatto JT. *Dumbing Us Down: The Hidden Curriculum of Compulsory Schooling*, p. 16

### Adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors (coxibs)

**Introduction:** Nonsteroidal anti-inflammatory drugs (NSAIDs) have many common and serious adverse effects, including the promotion of joint destruction. Paradoxically, these drugs *cause* or *exacerbate* the very symptoms and disease they are supposed to treat: joint pain and destruction. In a tragic exemplification of Orwellian newspeak<sup>32</sup>,

<sup>29</sup> Vetter et al. What do resident physicians know about nutrition? An evaluation of attitudes, self-perceived proficiency and knowledge. *J Am Coll Nutr*. 2008 Apr;27(2):287-98

<sup>30</sup> Halsted CH. The relevance of clinical nutrition education and role models to the practice of medicine. *Eur J Clin Nutr*. 1999 May;53 Suppl 2:S29-34

<sup>31</sup> Raman M, Violato C, Coderre S. How much do gastroenterology fellows know about nutrition? *J Clin Gastroenterol*. 2009 Jul;43(6):559-64

<sup>32</sup> Orwell G. 1984. Harcourt Brace Jovanovich: 1949. "Newspeak" is defined by the Merriam-Webster Dictionary (m-w.com) as "propagandistic language marked by euphemism, circumlocution, and the inversion of customary meanings" and as "a language designed to diminish the range of thought," in the novel *1984* (1949) by George Orwell.