

Some of the responses from the scientific community regarding recent JAMA report.

Review of Rizos et al JAMA 9/12/12, 308:10

By: Doug Bibus, PhD

The meta analysis review by Rizos et al is a culmination of a multiple number of studies examining the effects of omega 3 fatty acids on coronary outcomes. This study reported, in combining all studies, no significant effect of omega 3 fatty acids on many outcomes but did report overall reduced risk (as a trend) for:

1. All Cause Mortality 4%
2. Cardiac Death 9%
3. Sudden Death 13%
4. Myocardial Infarction 11%

While the statistical model employed by the authors did not find the aforementioned reductions significant, the fact that all (with exception of stroke) indicators of cardiovascular health were reduced as a trend, I find it difficult to share the conclusions of the authors regarding intake of omega 3 and find it highly inappropriate to expand the interpretation of this study to prevention while this study only looked at patients with established and mostly severe CVD disease.

Scientifically we have had a working and practical knowledge of the health benefits of omega 3 fatty acids since the studies of the Greenland Inuits. Greenlanders, while consuming high fat diets known to cause heart disease, did not appreciably die from heart disease due to their diet rich in omega 3 fatty acids. Thousands of reports since this time have documented basic science mechanisms, populational observations and outcomes in experimental human and animal models confirming the heart and health benefits of omega 3. The ground breaking MRFIT study reported dose dependent responses of dietary omega 3 in preventing CVD related death years ago.

Inflammation derived from arachidonic acid mediated metabolism by COX2 is often cited as a causal factor in the development of heart disease. Dr Bill Lands discovered the competitive inhibition of arachidonic acid by omega 3 fatty acids EPA and DHA.

Countless epidemiological studies have reported that fish consumption reduces our risk for developing heart disease. Are we now to assume that consumption of fish should be avoided and that omega 3 fatty acids do not protect us from heart disease?

From a practical standpoint what are the limitations of this study and why should we care?

1. Firstly, this study is attempting to collectively analyze several different studies with their own particular variability. Statistical models used in this meta-analysis make it difficult to predict and combine these studies for analysis. Significant findings are often difficult to achieve mathematically after adjusting for multiple factors.
2. This study examined the effects of omega 3 in people with established disease (SICK people) many with advanced heart disease. While the GISSI, DART and JELIS studies reported LARGE and SIGNIFICANT benefits at reducing risk and death with omega 3 fatty acids (in approximately 30,000 patients) not all studies have or will show demonstrate this. Does this

mean we should ignore the studies with benefit? Absolutely not. If a study reports increased risk of death with a drug and another does not, do we ignore the positive finding?

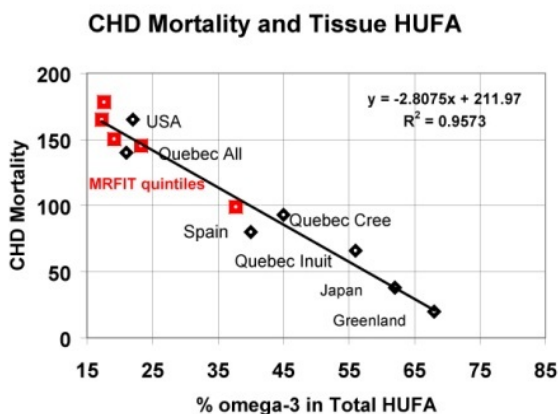
The ABC news report by Dianne Sawyer, unfortunately reported that (based on the present study) “omega 3 fatty acids could not prevent heart disease as once thought”. This is absolutely false. The study did not examine primary prevention and the response of ABC again highlights the ignorance of popular press in understanding and accurately reporting scientific data.

3. Patient and drug care for many of these studies utilized state of the art drug therapy. The opportunity for the benefits of omega 3 may be masked by current drug and medical therapy.
4. A major limitation of all studies cited in this analysis is patient compliance or how well we know that patients actually took their omega 3 supplements on a daily basis over the span of potentially several years. The authors of the study report that compliance for all studies was good at 80% or more but this is based on patient reporting, known to be plagued with false reports of intake and inconsistent intake especially over a multi-year study period. Similarly, the authors of this study did not factor compliance on the daily omega 3 dosage.

The most accurate way to measure compliance is by actually measuring omega 3 fatty acid levels in the blood of patients. They increase as your daily intake increases. Virtually none of these studies followed blood or tissue levels of omega 3. This simple blood test (omega 3) akin to cholesterol testing is typically overlooked. The real challenge for studies not reporting benefit of omega 3 is compliance and the extent that patients will lie about their actual intake or vary intake based on study time points.

5. Dosage of omega 3 in the reported studies. The dosage targeted by many studies investigating omega 3 are not sufficient to reach blood and tissue levels consistent with heart benefits. If a study targets 1g EPA and DHA and only has 60% compliance the effective dose is considerable less. The American Heart Association recommends 1 gram of EPA and DHA per day for people at risk. This level may not be adequate to treat people with active heart disease. A recent study reported that only 40% of patients reached optimal omega 3 blood levels on 1 gram of EPA and DHA per day. Similarly it should be noted that background diets rich in omega 6 INCREASE the requirement for omega 3 as these fatty acids actively compete for construction of tissue lipids.

The Lands' figure (below) illustrates the linear relationship between blood levels of omega 3 (x axis) and heart disease related mortality. A Lands' score of 50% correlates approximately with a 50% reduction in risk. For most Americans, a minimum dose of 2 to 3grams of omega 3 are required to reach 50% omega 3 in HUFA. Studies using lower doses may not accurately be powered to detect differences in primary outcomes.



Lands data: CHD mortality

Finally it should be noted that every study cited in the present study reported reduced risk for All-Cause Mortality (Death from any reason) that ranged from 4 to 70%. While this trend was not reported to be significant with the statistical models employed I feel it reflected strong bias on the part of the authors not to mention this. There is strong bias in many medical circles against dietary supplements that I feel are exhibited in this publication and resulting interviews in the popular press.

The past 40 years of research have demonstrated the value and essential nature of omega 3 fatty acids in promoting health especially cardiovascular health. Is it now appropriate, after this one study to completely disregard 40 years of research that collectively argues against these findings?

We should all be reminded of the young girl who was medically treated on an omega 3 deficient diet with venous nutrition following a gunshot wound to her stomach. After a few months on a high omega 6, deficient omega 3 diet, this girl developed paralysis, visual and cognitive impairment. Her symptoms worsened with time and it was quickly determined that her blood had almost no omega 3 fatty acids. This child responded to the addition of omega 3 fatty acids to her tube fed, fully resolving her symptoms of paralysis and visual and cognitive dysfunction. This is the classical study for the essentiality of omega 3 fatty acids by Hatch and Holman published in 1984.

Should you follow the advice of Dr Rizos in this paper to not take fish oil or omega 3 fatty acids to prevent heart disease? Absolutely not. Science firmly supports the cardiovascular protective effects of omega 3 for a healthy body, heart and mind.

Other responses:

'Flawed' omega-3 meta-analysis harms public health: GOED

By Stephen DANIELLS, 12-Sep-2012

A new meta-analysis that questioned the heart health benefits of omega-3s is 'flawed' and could deter consumers from taking fatty acid supplements and could be harmful to public health, says omega-3 trade association GOED.

Published yesterday in JAMA, data from 70,000 patients indicated that supplementation with omega-3 polyunsaturated fatty acids was not associated with a lower risk of cardiac death, sudden death, heart attack, or stroke.

"Our findings do not justify the use of omega-3 as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 PUFA administration," concluded researchers from the University Hospital of Ioannina in Greece.

Reaction

The conclusions were disputed by Adam Ismail, GOED executive director: "Given the flawed design of this meta-analysis, bypassing the advice of the American Heart Association or the 2010 Dietary Guidelines for Americans by stating that omega-3s are not cardioprotective, could be harmful to public health.

"GOED disputes the findings and urges consumers to continue taking omega-3 products if they are concerned about their heart."

Ismail added that researchers from Harvard University have estimated that 84,000 deaths a year could be prevented by adequate omega-3 consumption.

The heart health benefits of fish oil, and the omega-3 fatty acids it contains, are well-documented, being first reported in the early 1970s by Dr Jorn Dyerberg and his co-workers in The Lancet and The American Journal of Clinical Nutrition.

To date, the polyunsaturated fatty acids (PUFAs) have been linked to improvements in blood lipid levels, a reduced tendency of thrombosis, blood pressure and heart rate improvements, and improved vascular function.

Confounders

Harry Rice, PhD, VP of regulatory and scientific affairs for GOED, told NutraIngredients-USA that the authors failed to note that, with the passage of time, more and more cardio drugs have come onto the market and as a result a greater number of cardio patients are maintained on drug cocktails that include a greater number of drugs, making it difficult to demonstrate a cardiovascular benefit of yet one more substance (i.e. omega-3s).

"We know from the studies that have shown a benefit that future research in this area should only analyze studies that do not include confounding medications, are longer than two years in duration, and use dosages greater than 1-2 grams of omega-3s per day," he said. "Very few of the studies included in this meta-analysis met these criteria."

Meta-analysis

The Greece-based researchers analyzed data from 68,680 patients. The mean daily dose of omega-3 was 1.51 grams, with a mean EPA and DHA dose of 0.77 and 0.6 grams per day.

Analysis of the 7,044 deaths, 3,993 cardiac deaths, 1,150 sudden deaths, 1,837 heart attacks, and 1,490 strokes indicated that there were no statistically significant associations cardiovascular events or death.

“Randomized evidence will continue to accumulate in the field, yet an individual patient data meta-analysis would be more appropriate to refine possible associations related to, among others, dose, adherence, baseline intake, and cardiovascular disease risk group,” concluded the authors.

Recommendations

Duffy MacKay, ND, vice president, scientific and regulatory affairs for the Council for Responsible Nutrition (CRN) added that many of the studies included in the meta-analysis were conducted on diseased individuals already undergoing treatment with one or more drugs (e.g., statins), which may mask the less potent and more long-term effects of omega-3 fats.

“Along these lines, the researchers apparently did not examine within each individual study included in the meta-analysis whether individuals in the placebo group were sufficient or insufficient in their dietary intake omega-3 fats. Without that information, they could not have controlled for this variable.”

“Consumers should not be swayed by these results,” said Dr MacKay. “While people should be eating a diet high in fatty fish which contain these nutrients, the reality is that people are simply not doing this.

“Omega-3 supplements serve as an affordable, convenient and safe way to obtain omega-3 fatty acids and the array of health benefits they offer.”

Source: JAMA Volume 308, Number 10, Pages 1024-1033

“Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events - A Systematic Review and Meta-analysis”

Authors: E.C. Rizos, E.E. Ntzani, E. Bika, M.S. Kostapanos, M.S. Elisaf

http://newhope360.com/research/goed-disputes-jama-omega-3-meta-analysis?cid=nl_npi_daily

GOED disputes JAMA omega-3 meta-analysis

Sep. 12, 2012 8:28am Global Organization for EPA and DHA | Engredea News & Analysis

EMAILinShare.Comments 0 .GOED says the flawed design of a recent omega-3 meta-analysis leads to conclusions that could be harmful to public health.

The meta-analysis on omega-3s in the Journal of the American Medical Association is misleading and its findings are not warranted, according to the Global Organization for EPA and DHA (GOED).

"Given the flawed design of this meta-analysis, bypassing the advice of the American Heart Association or the 2010 Dietary Guidelines for Americans by stating that omega-3s are not cardioprotective could be harmful to public health," said Adam Ismail, GOED executive director. "GOED disputes the findings and urges consumers to continue taking omega-3 products if they are concerned about their heart."

This meta-analysis looked at people who have already suffered heart attacks or strokes rather than the general healthy population, and like some other recent studies, failed to account for the effect of cardiovascular disease medications consumed by subjects in the studies analyzed.

Harry B. Rice, PhD, vice president of regulatory and scientific affairs for GOED, commented, "Consider that cardiac patients today are prescribed multiple cardio drugs (such as cardiac glycosides, antiarrhythmics, antihypertensives, hypolipidemics, antianginals, anticoagulants, beta-blockers, calcium channel blockers, diuretics and/or vasodilators). There is a significant challenge in trying to determine if omega-3s can reduce cardiovascular disease risks if you are already giving patients a handful of other drugs that contribute to achieving that objective."

"We know from the studies that have shown a benefit that future research in this area should only analyze studies that do not include confounding medications, are longer than two years in duration, and use dosages greater than 1 to 2 grams of omega-3s per day," Rice said. "Very few of the studies included in this meta-analysis met these criteria."

GOED believes it is important for doctors and consumers to understand that the totality of the scientific evidence justifies the use of omega-3s for both people with diagnosed cardiovascular disease and those trying to prevent cardiovascular disease, said Ismail.

Researchers from Harvard University have estimated that 84,000 deaths a year could be prevented by adequate omega-3 consumption (goo.gl/fEakx) and governments and scientific groups around the world have established minimum recommended intakes based on this evidence (goo.gl/pP9uZ).

<http://www.drugstorenews.com/article/crn-debunks-omega-3-meta-analysis-inherently-inconclusive>

CRN debunks omega-3 meta-analysis as 'inherently inconclusive'

By Michael Johnsen

CHICAGO — As part of a meta-analysis spanning 70,000 patients, a study published in the Sept. 12 issue of JAMA determined supplementation with omega-3 fish oils was not associated with a lower risk in heart disease.

Lead researcher Evangelos Rizo of the University Hospital of Ioannina in Greece, concluded that omega-3 supplement recommendations may be overblown. "Our findings do not justify the use of omega-3 as a structured intervention in everyday clinical practice or guidelines supporting dietary omega-3 ... administration," he wrote.

However, given the many shortcomings around meta-analyses of a nutritional supplement's impact on disease states, "consumers should not discount the many proven benefits of omega-3 fatty acids in all stages of life," countered Duffy MacKay, VP scientific and regulatory affairs for the Council for Responsible Nutrition.

"This study does not change the current recommendations by authoritative bodies, such as the World Health Organization, American Heart Association and the U.S. National Academies of Science, who recommend adequate consumption of omega-3 fats," MacKay said.

The value in meta-analyses is found in combining comparable smaller clinical studies to assess whether similarities in the combined results exist.

The problem is in finding studies that are actually comparable. "This meta-analysis combined studies that were not comparable in their design ... which makes the results more skewed," MacKay noted. "Second, omega-3 fatty acids are vital nutrients and not drugs. Many of the studies included in the meta-analysis were conducted on diseased individuals already undergoing treatment with one or more drugs, such as statins, which may mask the less potent and more long-term effects of omega-3 fats."

Along these lines, the researchers apparently did not examine within each individual study included in the meta-analysis whether individuals in the placebo group were sufficient or insufficient in their dietary intake omega-3 fats, MacKay suggested.

"In this regard, studies on drugs are far simpler than those of nutrients [where] the treatment group gets the drug and the placebo group does not," he said. "With nutrients, if participants in the control group already have a diet sufficient in that substance, then it will be that much harder to demonstrate any benefit among the treatment participants. It is impossible for five researchers to control the diet of almost 70,000 patients over several years (particularly as a retrospective meta-analysis), as omega-3 fats are widespread throughout a variety of foods.