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A Misrepresented Meta-analysis
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CIRCULATIONAHA/2009/865667

This information is current as of March 16, 2009

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A Misrepresented Meta-analysis

Peer review is critical for ensuring that evidence assembled in a meta-analysis is complete and impartial. Regrettably, the recent AHA Advisory [1] relied heavily upon a one-line meta-analysis cited in a non peer-reviewed book chapter [2] to support its position that high intakes of omega-6 fatty acids reduce CHD. Unfortunately, the credibility of this advisory is undermined by four additional critical errors.

1) The AHA Advisory mistakenly cited the Sydney Diet-Heart Study [3] when referring to Gordon's meta-analysis [2] and its ascribed conclusion that "PUFA lowered the risk of CHD events by 24%" [1]. The Sydney study did not report CHD events and was not included in Gordon's analysis of CHD events. Importantly, the study did report that 39 of 221 (18%) high omega-6 LA dieters died within 5 years versus only 28 of 237 (12%) of controls, and that 63 of 67 (94%) of these deaths were due to CV disease [3]. This 49% increased death rate in the high-LA group warrants attention and discussion in any balanced review of published evidence.

2) Although the AHA Advisory [1] criticizes other studies for failing to distinguish between "distinct effects" of omega-3 and omega-6 fatty acids, it commits this error throughout. One example is attributing "almost entirely omega-6 PUFA" to three trials that provided more than 2% of energy as omega-3 ALA and one that instructed dieters to consume more seafood and supplied them with "considerable quantities of Norwegian sardines canned in cod liver oil" [4], major sources of omega-3 EPA and DHA.

3) The AHA Advisory imprecisely contends that its analysis pertains to trials that "evaluated the effects of replacing saturated fatty acids with PUFAs" [1] despite its citation of trials where experimental diets displaced large quantities of trans fatty acid-rich partially hydrogenated oils. For instance, in the two decades before the Oslo Diet-Heart Study, Oslo males had an alarming 7-fold increased incidence of first myocardial infarction (from 9.0 per 10,000 in 1945 to 64.9 per 10,000 in 1961) [4]. This rapid rise coincided with pervasive use of partially hydrogenated fish and vegetable oil margarines, accounting for 65 grams per person per day (>25 % of energy) at study onset [4]. Importantly, experimental dieters replaced these margarines with non-hydrogenated oils, while the control group diet continued consumption.

4) The AHA Advisory failed to indicate that the Rose Corn Oil Trial [5] gives a rare opportunity to evaluate the specific effects of increased LA, because corn oil has little omega-3 ALA. Here, 28 post-myocardial infarction dieters substituted corn oil for animal fats and fried foods, and two years later, 5 of 28 (18%) had died and 48% had a serious cardiac event. In contrast, the 26 control dieters made no changes, and only 1 of 26 (4%) died and only 25% had a serious cardiac event. Rose et al. concluded that corn oil "cannot be recommended as a treatment of ischemic heart disease" because it is "most unlikely to be beneficial, and it is possibly harmful".

Acknowledgements: None
Funding Sources: None
Disclosures: None
Abbreviations (if necessary): linoleic acid (LA), alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), polyunsaturated fatty acid (PUFA)

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From suggestion to admonition without direct data

Joseph R. Hibbeln

CIRCULATIONAHA/2009/866566

This information is current as of March 18, 2009

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Unfortunately a recent AHA advisory[1] fails to acknowledge decades of experience with aspirin, which has well-known anti-inflammatory and anti-thrombotic actions by decreasing the formation of n-6 eicosanoids from arachidonate (AA). The advisory also neglects massive evidence for competing actions in metabolism of omega-3 and omega-6 acids that affect human physiology, especially at intakes below 5 en% linoleate (LA)[2]. Rather, the advisory offers only fragmentary comments that eicosanoids have multiple actions[3,4]. Neglected are the disproportionately stronger inflammatory and aggregatory actions of eicosanoids derived from AA that occur with relative deficits of eicosanoiate, docosapentanaoate and docosahexanoate in the phospholipid precursors of eicosanoid generation[3]. For example, LTB_4 derived from AA is much more potent inflammatory and aggregatory than LTB_5 derived from EPA[4]. The AHA advisory ignores the major role of LA as the precursor of tissue AA, stating "At present, little direct evidence supports a net pro-inflammatory, pro-atherogenic effect of LA in humans". The advisory fails to inform the public that an important tissue indicator of CVD risk the 'Omega-3 Index'[5], reflects the proportion of EPA and DHA in erythrocytes, a representative phospholipid eicosanoid precursor pool. The Omega-3 Index is regarded[5] as superior to LDL as a biomarker predicting cardiovascular mortality. Paradoxically, the advisory reports that increasing LA intakes decreases EPA accretion, (i.e. lowers the Omega-3 Index and increases CVD risk), but implies without comparative quantitation that lowering LA intakes would elevate LDL levels and increase net CVD risk. However, lowering LA by LNA substitution could maintain PUFA intakes and result in a more favorable Omega-3 Index [2].

The advisory unfortunately moves from suggestive and highly conditional interpretations to the unsupported clinical admonition that "To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD." No quantitative risk-benefit assessment of this admonition is provided. The advisory concludes that published observational studies only "suggest an overall modest benefit of omega-6 PUFA intake on CHD risk" without quantifying clinical effect size or statistical significance. The advisory alleges that "The data also suggest that higher intakes appear to be safe and may be even more beneficial (as part of a low–saturated-fat, low-cholesterol diet)" without specification of the mechanistic dietary component. The advisory notes that "increasing omega-3 PUFA tissue levels

does reduce the risk for CHD", but follows with the undocumented suggestion that "evidence considered here suggests that it [lowering LA] would have the opposite effect." The advisory cites no valid evidence from randomized clinical trials that evaluated intakes below 5 en% LA and in contrast states it considered clinical interventions ranging only from 11-21 en % . None-the-less it concludes that "Aggregate data from randomized trials, case-control and cohort studies, and long-term animal feeding experiments indicate that the consumption of at least 5% to 10% of energy from omega-6 PUFAs reduces the risk of CHD relative to lower intakes". Without explicitly controlled clinical evidence evaluating intakes between 1-4 en% LA, the advisory offers no credible advice regarding possible clinical benefits of lowering LA intakes.

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letter to the editor
Bill Lands
CIRCULATIONAHA/2009/866434

This information is current as of March 17, 2009

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CIRCULATIONAHA/2009/866434

A Letter to the Editor:

A recent AHA advisory[1] incorrectly cited Mohrhauer and Holman[2] to support an undocumented claim that "the production of omega-6 AA from LA is tightly regulated" and that “wide variations in dietary LA (above minimal essential intakes) do not materially alter tissue AA content.” In contrast, Mohrhauer and Holman clearly showed that when dietary linoleate (LA) ranged from 0 to 4.87 % of energy (en %), the accumulation of arachidonate (AA) in liver lipids[2] and erythrocytes[3] ranged widely: from 1.8 to 14.7 wt% and 5.6 to 18.74 wt%, respectively. The evidence[2, 3] shows dietary intakes of LA or LNA below 3 en % have marked impacts on tissue proportions of 20- and 22-carbon highly unsaturated fatty acids (HUFA) as competitive metabolic processes have not yet ‘plateaued’. In a related paper[4], Mohrhauer and Holman emphasized competitive hyperbolic interactions by which dietary LA and ALA interfere with accumulation of each other's elongated and desaturated HUFA in tissues. As a result, data comparing dietary intakes of 11 -21 en% LA on tissue n-3 and n-6 HUFA compositions cannot be linearly extrapolated to results for dietary intakes below 5 en% LA as implied in the advisory.

The advisory failed to acknowledge that competitive interactions[4] decrease the proportions of n-6 acids among the tissue HUFA when dietary n-3 acids increase[5]. The competing metabolic interactions allow assessment of an individual’s omega-3 status by using plasma, erythrocytes or whole blood, any of which can give very useful estimates of the likely risk for several disease states caused by imbalanced tissue levels of n-3 and n-6 fatty acids. Stark et al[5] compared several formats for expressing omega-3 status, finding that the percentage of n-3 highly unsaturated fatty acids in total HUFA is a useful biomarker for omega-3 fatty acid status in tissues. Increasing the percent of n-3 in HUFA inevitably decreases the percent of n-6 in HUFA. The advisory asserts that LA “does not materially alter AA content”, however the proportion of n-6 in HUFA decreases as n-3 in HUFA increases. The advisory recognizes that dietary AA can affect tissue AA levels. Similarly, dietary

intakes of 0.5 en % n-3 HUFA can be predicted to markedly impact tissue HUFA proportions and obscure the effects of varied dietary LA intakes on n-6 HUFA composition.

The AHA advisory creates confusion when it combines the idea that "higher omega-6 PUFA intakes can inhibit the conversion of α-linolenic acid to eicosapentaenoic acid" with an assertion that "such conversion is already quite low". However, that conversion of α-linolenate (ALA) to eicosapentaenoate (EPA) was assessed in the presence of 5-10-fold greater levels of competing dietary LA known to cause low conversion[4]. The AHA advisory compounds misunderstanding by combining the idea that "increasing omega-3 PUFA tissue levels does reduce the risk for CHD" with an undocumented suggestion that "decreasing omega-6 levels" "would have the opposite effect". Misrepresentation of reciprocal competitions in pathways of n-6 LA and n-3 ALA metabolism seriously reduces the credibility of the AHA advisory and its usefulness for the general public.

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Where is the Science? The Science Advisory on Omega-6 Polyunsaturated Fats
Evelyn Tribole
CIRCULATIONAHA/2009/868448

This information is current as of March 25, 2009

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Where's the Science? AHA's Science Advisory on Omega-6 Fats Polyunsaturated Fatty Acids

There are several sweeping claims, based on research taken out of context. This letter highlights only a few of the problems.

Harris et al.[1] cite a series of metabolic studies in which healthy men were fed a diet high in arachidonic acid (AA) and claim there was no evidence of harmful effects [2]. Yet, that's not what the data show.

When the men ate a high AA diet (1.5 grams/day), they experienced a marked increase in AA-derived vasoactive compounds, compared to when they ate a stabilizing diet with 210 mg/d of AA. There was 41% more thromboxane (TXA2), a powerful inducer of platelet aggregation and vasoconstriction and 27% more prostacyclin, compared to their baseline levels. The researchers called this magnitude of increase "remarkable" and concluded that increasing dietary AA could increase the risk of thrombosis [2].

The selective omission of this conclusion is especially troubling, given that most cases of myocardial infarction are due to the formation of an occluding thrombus on the surface of the arterial plaque. [3] Also problematic, is the size and duration of this study series, which had only 10 subjects, who were fed the high AA diet for a net of a 50-day period--hardly a basis from which to generalize help or harm to the public.

Ferrucci's inChianti study was cited as another example of no harm, because the subjects with the highest (AA) blood levels had lower pro-inflammatory markers and higher anti-inflammatory markers [4]. Once again, an important detail is ignored—the subjects from this Mediterranean region of Italy eat a low omega-6 PUFA diet, averaging 7 grams of *total* PUFA/day.

In this context, it is not surprising that plasma AA was associated with beneficial inflammation biomarkers--because it does so in the presence of eating a low omega-6 diet, providing 3 percent of energy from omega-6 PUFA. Yet, the AHA advisory urges nearly double this amount of omega-6 fat

for Americans of at least 5% to10% of energy from omega-6 PUFAs (12 grams for women and 17 grams for men).

AHA's advisory continues the problematic trend identified by Tricoci et al [5], which found that a large proportion of recommendations in ACC/AHA guidelines are based on the lowest category of evidence, "expert" opinion, in formulating guidelines with little empirical evidence. Health care professionals are well-advised to heed Tricoci's recommendation--to exercise caution when considering guidelines not supported by solid evidence, which unfortunately is the case with this omega-6 PUFA advisory.

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To the Editor

We do not disagree with most of the points raised by Ramsden that highlight some limitations of the relatively few and older randomized controlled trials (RCTs) that have aimed to test the effect of omega-6 polyunsaturated fatty acids (FAs) on coronary heart disease (CHD) events. We clearly specified in the Science Advisory[1] that many of these trials had design limitations, including for example "use of vegetable oils that also contained the plant omega-3 alpha-linolenic acid," and "simultaneous recommendations to increase fish and cod liver oil use." Nonetheless, this is the best RCT evidence currently available, and, with the exception of marine omega-3 FA, the only set of RCTs of clinical CHD outcomes for which any dietary factor has shown benefits or trends toward benefits. However, Ramsden is mistaken that either the Advisory's conclusions or the evidence for cardiovascular benefits of omega-6 FA rely heavily on these data. As opposed to tests of drug treatments, understanding the effects of diet and other lifestyle behaviors such as physical activity and smoking on cardiovascular risk cannot be based solely on RCTs of clinical CHD outcomes. The challenge of using the RCT paradigm to test the role of these factors in disease causation include difficulties in establishing appropriate control diets or behaviors; maintaining blinding and compliance; testing relevant doses and durations of effects; and including appropriate populations and stages of disease. Thus, effects of diet and other lifestyle behaviors should be evaluated based on the totality of evidence, including RCTs of clinical outcomes, well-performed observational studies of clinical outcomes, and short-term RCTs of surrogate risk factors. It is the full spectrum of the data, as summarized in the Advisory, that clearly supports the cardiovascular benefits of omega-6 FA consumption.

We also welcome the opportunity to respond to Hibbeln, Lands, and Tribole . The concepts that underlie their concerns may be summarized in the following series of statements:

1. Higher linoleic acid (LA) intakes = higher tissue arachidonic acid (AA) levels.

2. Higher tissue AA = enhanced eicosanoid response to inflammatory stimuli.

3. Enhanced eicosanoid response to inflammatory stimuli = higher risk for CHD.

4. Lower LA + higher α-linolenic acid (ALA) intakes = higher tissue eicosapentaenoic acid (EPA) levels.

5. Higher tissue EPA = higher omega-3 index (erythrocyte EPA+DHA).

6. Higher omega-3 index = lower risk for CHD.

7. Aspirin use = inhibition of eicosanoid synthesis from AA.

8. Inhibition of eicosanoid synthesis from AA = reduced platelet aggregation and inflammation.

9. Reduced platelet aggregation and inflammation = less CHD.

10. Therefore, to reduce risk for CHD, reduce LA intakes.

Understanding the misunderstandings requires careful consideration of each of these statements to determine which are correct, which need to be contextualized, which derive from animal studies, and which are simply wrong. Several of these issues were addressed, with reference to published literature, in the Advisory, and others in a letter [2] responding to similar concerns raised by the same 3 inquirers.

Statement 1 is true if you are a rat consuming a fat-free diet supplemented with ethyl linoleate. Otherwise, in human diets, variations in LA intake do not significantly affect tissue AA levels. As noted in the Advisory, very little (i.e., about 0.2%) LA is actually converted to AA based on human tracer studies [3]. One study not included in the Advisory is illustrative [4]. In 1988, we fed 25 subjects 18 g/d of fish oil (6 g/d of EPA+DHA) and compared its effects to those of a "placebo" – 18 g of safflower oil – which provided about 14 g/d of LA. In other words, we nearly doubled current LA intakes. After 6 weeks on safflower oil, there was no difference in plasma or platelet AA levels, and we found no change in any measure of platelet function (including bleeding times, response to 3 different agonists, and thromboxanes B_2 generation). LDL-cholesterol levels were, however, lowered in patients with combined dyslipidemia. These data, in conjunction with other citations in the Advisory, indicate that statements 1 and 2 are at best, questionable. Statement 3 is conditionally true: there clearly is an inflammatory component to CHD as noted in the Advisory, although the role of eicosanoids per se is less clear.

Statements 4-6 are generally true. The omega-3 index is inversely associated with risk for fatal CHD [5]. However, one must examine the *overall* effect of increased LA + decreased ALA on this marker. Liou et al. [6] fed 22 subjects diets high (10.5% energy) and low (3.8% energy) in LA while holding ALA constant (1% energy) for 2, 4-week periods in a cross over design. They assessed the effects on plasma phospholipid FA composition. While the high LA diet did lower EPA levels from about 0.9% to 0.5% of total FAs, DHA levels were *increased* by the high LA diet from 2.9% to 3.4% of total FAs. Thus, the omega-3 index was not affected by a high LA diet. Nor, it should be noted, were AA levels. But even if high LA diets did lower the omega-3 index, there are independent, cardioprotective actions of LA itself (e.g., lowering serum cholesterol and possibly improving endothelial function and insulin resistance) that could more than compensate for the reduction in omega-3 levels. One cannot assume that CHD risk changes in lock-step with variations in any one risk factor.

As regards statements 7-9, it is well-known that aspirin treatment reduces the synthesis of thromboxane (indeed, of all cyclo-oxygenase products) and reduces risk for atherothrombosis. However, this does not mean that membrane AA levels are rate limiting for eicosanoids synthesis, nor that "proinflammatory" eicosanoids (e.g., thromboxane A_2, leukotriene B_4 and prostaglandin E_2) are the only eicosanoids produced in response to an inflammatory stress; AA also gives rise to important anti-inflammatory metabolites like the epoxyeicosatrienoic acid [7] and lipoxin A [8]. More to the point, these statements have little direct bearing on the relations between LA consumption and inflammation, a topic specifically addressed by Fritsche [9].

Rather than reasoning from indirect data, the authors of the Advisory chose to focus on the evidence for effects of LA on established CHD risk factors and actual CHD events in humans. Based largely on prospective cohort studies and randomized controlled trials in humans - all undergirded by similar results in long-term primate feeding studies – we found that higher intakes of LA are cardioprotective. In

support of this conclusion is a recent prospective cohort study involving over 2000 men followed for over 30 years in which lower serum levels of LA were significantly associated with *increased*, not decreased, risk for death [10]. In addition, a pooled analysis of 11 prospective studies including 344,696 participants from the U.S., Europe, and Israel found that only replacement of saturated fat with polyunsaturated fat (predominantly LA), not monounsaturated fat or carbohydrate, was associated with lower incidence of CHD [11]. We agree that, although randomized trials have shown LA intakes of >10% energy to be cardioprotective relative to intakes of 4-5% energy, there have been no endpoint studies testing the effects of very low levels (e.g., <2% energy) against current LA intake levels (e.g., 6% energy). Therefore, dogmatic statements regarding either the benefits or harms of such low intakes cannot be (and were not) made. However, in 6 of the 11 cohort studies described above, the 10th percentile LA consumption level was below 4% energy, even as low as 1.7% energy. Therefore, there are human data supporting a direct, protective effect of higher polyunsaturated fat (largely LA) consumption across virtually all intake strata.

For statement 10 to be true, one would have to dismiss the findings of large controlled trials and prospective cohort studies in humans in favor of extrapolations from effects of aspirin, selective changes caused by short-term high-dose AA feeding, the theoretical impact on CHD risk from small changes in an emerging risk marker, and experiments with rats. The authors of the Science Advisory did not believe that this option would lead to accurate or useful conclusions, as the former data set is far more compelling and relevant than the latter.

The perspectives reflected in these Letters to the Editor focus on relatively tangential observations that have too easily distracted from the central finding, a finding supported by a robust and coherent dataset that has accrued over decades, that omega-6 FAs are cardioprotective. As noted above, it is the full data set that forms the basis of the American Heart Association's recommendation that a heart healthy diet should include, in addition to omega-3 FAs, at least 5%-10% of energy as omega-6 FAs.

William S. Harris, PhD, FAHA, Chair; Dariush Mozaffarian, MD, DrPH, FAHA; Eric Rimm, ScD, FAHA; Penny Kris-Etherton, PhD, FAHA; Lawrence L. Rudel, PhD, FAHA; Lawrence J. Appel, MD, MPH, FAHA; Marguerite M. Engler, PhD, FAHA; Mary B. Engler, PhD, FAHA; Frank Sacks, MD, FAHA

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