

TABLE 1Fatty acid pattern in tissue phospholipids of n-3 fatty acid-depleted and control female rats¹

	20:4n-6		22:1n-9	
	Control rats	n-3 Depleted rats	Control rats	n-3 Depleted rats
	% by wt		% by wt	
Brain	12.04 ± 0.30 (16)	18.00 ± 0.30 (18) ²	0.23 ± 0.03 (16)	0.16 ± 0.03 (18)
Liver	29.52 ± 0.34 (16)	38.31 ± 0.26 (18) ²	0.17 ± 0.02 (16)	0.23 ± 0.03 (18)
Soleus muscle	18.67 ± 0.26 (16)	28.82 ± 0.25 (18) ²	0.22 ± 0.07 (16)	0.12 ± 0.03 (18)
Heart muscle	22.93 ± 0.31 (16)	32.33 ± 0.42 (18) ²	0.17 ± 0.03 (16)	0.17 ± 0.02 (18)
Endocardium	24.20 ± 0.38 (3)	31.54 ± 0.50 (11) ²	0.40 ± 0.05 (3)	0.08 ± 0.04 (11) ²

¹ All values are $\bar{x} \pm SE$; *n* in parentheses.² Significantly different from control rats, *P* < 0.005.

Yvon A Carpentier
Laurence Portois
Willy J Malaisse

L Deloyers Laboratory of Experimental Surgery
Avenue J Wybran 40
Université Libre de Bruxelles
1070 Brussels
Belgium
E-mail: nutrisub@ulb.ac.be

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α -Linolenic acid and fish oil n-3 fatty acids and cardiovascular disease risk

Dear Sir:

In evaluating the cardiovascular merits of n-3 fatty acids, Wang et al (1) appropriately sought the best available evidence and used randomized controlled human trials (RCTs) as their benchmark. As they showed, such trials designed to examine the cardiovascular effects of α -linolenic acid (ALA) have not been done to everyone's satisfaction. Because they clearly defined at the outset what they meant by "high-quality evidence," we cannot disagree with their conclusion there is no "high-quality evidence to support a beneficial effect of ALA." What we reject however is that, once they make this initial point, Wang et al slide down a slippery slope toward broad enthusiasm for fish oils and outright dismissal of ALA. Neither position is supported by the existing literature.

First, it is incorrect to say that Dolecek's analysis of the MRFIT study (2) showed no association between ALA and cardiac death; Dolecek's analysis showed that, as a percentage of energy intake and in g/d, ALA was significantly negatively associated with cardiovascular, cancer, and all-cause mortality. Second, acute, short-term experiments showed that ALA has antiarrhythmic effects (3) and reduces platelet aggregation (4), and both effects could plausibly contribute significantly toward reduction of cardiovascular and all-cause mortality. Third, for all its possible confounders, the Lyon study (5) was a randomized controlled secondary prevention trial that, supported by a blood fatty acid analysis, clearly implicated ALA in risk reduction of cardiovascular disease and death. Hence, these diverse examples are consistent with cardiovascular benefits of

ALA. They can in no way substitute for placebo-controlled RCTs, but they show that grounds exist for well-controlled trials to assess whether ALA reduces the risk of cardiovascular death.

Furthermore, Wang et al cite the concern with regard to ALA and prostate cancer in the absence of confirmatory RCT evidence but downplay some potentially equally important adverse cardiovascular effects of fish oils where RCTs exist. For instance, they cite the recent study by Raitt et al (6), which was conducted in subjects with an implantable cardioverter defibrillator, and mention that the risk of death did not change but downplayed the significantly increased risk of ventricular tachycardia or ventricular fibrillation when consuming 1.3 g fish oil n-3 fatty acids/d. At the time of publication of the article by Wang et al, they may not have been aware that Frost and Vestergaard (7) showed in a population study that Danes who consumed 1.29 g fish oil n-3 fatty acids/d (the top quintile) had a 34% higher rate of atrial fibrillation than did those who consumed 0.16 g fish oil n-3 fatty acids/d (the bottom quintile).

We are not saying that these reports of adverse cardiovascular outcomes with consumption of fish oils constitute sufficient evidence to dismiss the beneficial effects seen in controlled trials. We are saying that a systematic review purporting to give an "evidence-based review" of the cardiovascular effects of n-3 fatty acids should not conflate an absence of well-controlled trials examining cardiovascular effects of ALA with an absence of evidence that ALA has any benefits for the cardiovascular system. Furthermore, not all would agree that the arrhythmogenic effects of fish oils in certain cardiac patients are "minor;" the adverse effects of all n-3 fatty acids should be given appropriate and similar scrutiny. Clearly, additional ALA trials are overdue considering the strength of the existing evidence and the seriousness of the disease.

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Eddie Vos

Courser Road
Sutton, QC
Canada
E-mail: vos@health-heart.org

David JA Jenkins

Department of Nutritional Sciences
University of Toronto
Toronto, ON
Canada

Stephen C Cunnane

Research Center on Aging
University of Sherbrooke
Sherbrooke, QC
Canada

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very high intakes of both ALA (6 g/d) and eicosapentaenoic acid + docosahexaenoic acid (EPA + DHA; 5.2 g/d) were provided, neither of which has been shown at these doses to be cardioprotective. In addition, no effects were seen on plasma lipids for either ALA or EPA + DHA, and the minor effects on platelet aggregation do not explain the reduction in cardiac events that have been observed with ≤ 1 g EPA + DHA.

The Lyon Heart Study (5) was not designed to show and cannot be construed as showing that ALA was the agent responsible for the reduction in clinical events. Multiple variables were manipulated in that trial. Simply because serum concentrations of ALA were inversely associated with a reduced risk does not indicate that ALA that was responsible for the reduced risk. Association is not cause and effect, and a "true-true-and-unrelated" association is always possible.

Experimental studies conducted in animals and in vitro studies conducted in humans that focus on intermediate outcomes are important to uncover the mechanisms involved in the potential beneficial cardiovascular outcomes of n-3 fatty acid consumption in humans. The findings in the articles referred to by Vos et al support the hypothesis that ALA is cardioprotective and are reinforced by recent epidemiologic data (6, 7). However, these promising results must still be directly tested in human randomized controlled trials, rather than the benefits to humans assumed. Whether ALA has similar beneficial cardiovascular effects through diet or as supplements remains to be explored. Direct evidence does not support the view that ALA reduces the risk of cardiovascular events.

JL and AHL have no conflict of interest to declare. WSH is a scientific advisor to OmegaMetrix LLC, Monsanto, CardioTabs, and TherRx.

Joseph Lau

Reply to E Vos et al

Dear Sir:

We thank Vos et al for their comments on our article (1), but we disagree with their statement that our review showed "broad enthusiasm for fish oil and outright dismissal of ALA [α -linolenic acid]." Our systematic review focused on the health effects of dietary n-3 fatty acids on clinical cardiovascular outcomes in humans and evaluated available evidence according to predefined questions. To minimize bias, conclusions were drawn based on the studies that met predefined criteria.

Vos et al did not disagree with the criteria we used to determine the quality of evidence. However, they seem to differ in what they would consider to be valid evidence by referencing several studies that did not meet our predetermined criteria. They refer to an acute, short-term experimental study in dogs to illustrate the potential beneficial antiarrhythmic effects of α -linolenic acid (ALA) (2). In the study by Billman et al (2), ALA was infused intravenously in an exercise-ischemia model of ventricular fibrillation. In fact, we reviewed this study in a separate article addressing the question of the effect of n-3 fatty acids on selected arrhythmia outcomes in animal models (3). Even if evidence from a dog study could be used to infer a benefit in humans, the experimental setting is highly unphysiological. Furthermore, whether such high plasma ALA concentrations are even achievable in a human consuming ALA is unknown (however, it is very unlikely).

Vos et al also cited the study by Freese (4), in which ALA supplementation reduced in vitro measures of platelet aggregation, as evidence that the reduction in platelet aggregation plausibly contributed to a reduction in the risk of cardiovascular events. In this study,

Institute for Clinical Research and Health Policy Studies
Tufts-New England Medical Center
750 Washington Street
Box 63
Boston, MA 02111
E-mail: jlau1@tufts-nemc.org

William S Harris

Nutrition and Metabolic Disease Research Institute
Sanford Research—University of South Dakota
Department of Medicine
Sanford School of Medicine
University of South Dakota
Vermillion, SD

Alice H Lichtenstein

Cardiovascular Nutrition Laboratory
Jean Mayer USDA Human Nutrition Research Center on
Aging
Tufts University
Boston, MA

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