

## Omega-6 Fatty Acids and Risk for Cardiovascular Disease A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention

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

A large body of literature suggests that higher intakes of omega-6 (or n-6) polyunsaturated fatty acids (PUFAs) reduce risk for coronary heart disease (CHD). However, for the reasons outlined below, some individuals and groups have recommended substantial reductions in omega-6 PUFA intake.<sup>1-4</sup> The purpose of this advisory is to review evidence on the relationship between omega-6 PUFAs and the risk of CHD and cardiovascular disease.

### Omega-6 PUFAs

Omega-6 PUFAs are characterized by the presence of at least 2 carbon-carbon double bonds, with the first bond at the sixth carbon from the methyl terminus. Linoleic acid (LA), an 18-carbon fatty acid with 2 double bonds (18:2 omega-6), is the primary dietary omega-6 PUFA. LA cannot be synthesized by humans, and although firm minimum requirements have not been established for healthy adults, estimates derived from studies in infants and hospitalized patients receiving total parenteral nutrition suggest that an LA intake of  $\approx 0.5\%$  to  $2\%$  of energy is likely to suffice. After consumption, LA can be desaturated and elongated to form other omega-6 PUFAs such as  $\gamma$ -linolenic and dihomo- $\gamma$ -linolenic acids. The latter is converted to the metabolically important omega-6 PUFA arachidonic acid (AA; 20:4 omega-6), the substrate for a wide array of reactive oxygenated metabolites. Because LA accounts for 85% to 90% of the dietary omega-6 PUFA, this advisory focuses primarily on this fatty acid, recognizing that dietary AA, which can affect tissue AA

levels,<sup>5</sup> may have physiological sequelae.<sup>6-8</sup> LA comes primarily from vegetable oils (eg, corn, sunflower, safflower, soy). The average US intake of LA, according to National Health and Nutrition Examination Survey 2001 to 2002 data for adults  $\geq 19$  years of age, is 14.8 g/d.<sup>9</sup> On the basis of an average intake of 2000 kcal/d, LA intake is 6.7% of energy. AA ( $\approx 0.15$  g/d) is consumed preformed in meat, eggs, and some fish.

### Omega-6 PUFAs and Inflammation

Arguments for reduced LA intakes are based on the assumption that because CHD has an inflammatory component<sup>10</sup> and because the omega-6 fatty acid, AA, is the substrate for the synthesis of a variety of proinflammatory molecules, reducing LA intakes should reduce tissue AA content, which should reduce the inflammatory potential and therefore lower the risk for CHD. The evidence, derived primarily from human studies, regarding this line of reasoning is examined below.

AA is the substrate for the production of a wide variety of eicosanoids (20-carbon AA metabolites). Some are proinflammatory, vasoconstrictive, and/or proaggregatory, such as prostaglandin E<sub>2</sub>, thromboxane A<sub>2</sub>, and leukotriene B<sub>4</sub>. However, others are antiinflammatory/antiaggregatory, such as prostacyclin, lipoxin A<sub>4</sub>,<sup>11</sup> and epoxyeicosatrienoic acids.<sup>12</sup> Epoxyeicosatrienoic acids are fatty acid epoxides produced from AA by a cytochrome P450 epoxygenase. Epoxyeicosatrienoic acids also have important vasodilator properties via

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hyperpolarization and relaxation of vascular smooth muscle cells.<sup>13</sup> Importantly, because the production of AA from LA is tightly regulated,<sup>14</sup> wide variations in dietary LA (above minimal essential intakes) do not materially alter tissue AA content.<sup>15</sup> In tracer studies, the extent of conversion of LA to AA is  $\approx 0.2\%$ .<sup>16</sup>

In studies with vascular endothelial cells, omega-6 PUFA had antiinflammatory properties, suppressing the production of adhesion molecules, chemokines, and interleukins, all key mediators of the atherosclerotic process.<sup>17</sup> In human studies, higher plasma levels of omega-6 PUFAs, mainly AA, were associated with decreased plasma levels of serum proinflammatory markers, particularly interleukin-6 and interleukin-1 receptor antagonist, and increased levels of antiinflammatory markers, particularly transforming growth factor- $\beta$ .<sup>18</sup> When healthy volunteers were given  $\approx 7$  times the usual intake of AA (ie, 1.5 g/d) in a 7-week controlled feeding study, no effects on platelet aggregation, bleeding times, the balance of vasoactive metabolites, serum lipid levels, or immune response were observed.<sup>5-8</sup> Likewise, in a recent study from Japan, AA supplementation (840 mg/d for 4 weeks) had no effect on any metabolic parameter or platelet function.<sup>19</sup> Consistent with this, in observational studies, higher omega-6 PUFA consumption was associated with unaltered or lower levels of inflammatory markers.<sup>20</sup>

Diets high in LA can increase the *ex vivo* susceptibility of low-density lipoprotein (LDL) to oxidation,<sup>21</sup> and oxidized LDL can promote vascular inflammation.<sup>22</sup> Therefore, oxidized LDL may play some role in the etiology of CHD.<sup>23</sup> However, the extent of LDL oxidation at higher LA intakes (5% to 15% of energy) has not been established, and its clinical relevance is in question owing to the general failure of antioxidant treatments to mitigate CHD risk in most randomized trials.<sup>24</sup> At present, little direct evidence supports a net proinflammatory, proatherogenic effect of LA in humans.<sup>22,25,26</sup>

### **Omega-6 PUFA Consumption and Other CHD Risk Factors/Markers**

The cholesterol-lowering effect of LA is well established from human trials. In a meta-analysis of 60 feeding studies including 1672 volunteers, the substitution of PUFA (largely omega-6, varying from 0.6% to 28.8% energy) for carbohydrates had more favorable effects on the ratio of total to high-density lipoprotein cholesterol (perhaps the best lipid predictor of CHD risk) than any class of fatty acids.<sup>27</sup> Higher plasma PUFA levels are associated with a reduced ratio of total to high-density lipoprotein cholesterol,<sup>28</sup> and epidemiologically, the replacement of 10% of calories from saturated fatty acid with omega-6 PUFA is associated with an 18-mg/dL decrease in LDL cholesterol, greater than that observed with similar replacement with carbohydrate.<sup>29</sup> These findings confirm an LDL-lowering effect of omega-6 PUFA beyond that produced by the removal of saturated fatty acids. Favorable effects of LA on cholesterol levels are thus well documented and would predict significant reductions in CHD risk. Additionally, higher LA intakes may improve insulin resistance<sup>30</sup> and reduce the incidence of diabetes mellitus,<sup>31</sup> and higher serum LA levels are associated with lower blood

pressure.<sup>32</sup> Nevertheless, not all studies support a beneficial effect of LA on CHD risk markers. For example, an angiographic study reported a direct association between PUFA intakes and luminal narrowing in women with CHD.<sup>33</sup> However, effects on markers do not always translate into effects on actual clinical end points; thus, it is essential to evaluate the relations between LA consumption and CHD events.

### **Omega-6 PUFA Consumption and CHD Events: Observational Studies**

#### **Ecological Studies**

Cross-cultural, cross-sectional, and time-trend studies examining omega-6 PUFA intake and CHD risk demonstrate equivocal results.<sup>34,35</sup> Among the 4584 subjects in the National Heart, Lung, and Blood Institute Family Heart Study, the prevalence of coronary artery disease was  $\approx 66\%$  higher at LA intakes of 1.8% compared with 5.3%.<sup>36</sup> The weaknesses of these study designs for evaluating diet-disease relations are well documented,<sup>37</sup> and most evaluated only total PUFA intake, failing to distinguish between omega-3 and omega-6 PUFAs and their potentially distinct effects. Given these limitations, firm conclusions cannot be drawn from these studies.

#### **Case-Control Studies**

In a meta-analysis of 25 case-control studies (including 1998 cases and 6913 controls) evaluating blood/tissue omega-6 PUFA content and CHD events, LA content was inversely associated with CHD risk, whereas AA was unrelated to CHD risk.<sup>38</sup> Even very high LA intakes have been associated with lower risk; in 1 study in Israel,<sup>39</sup> where 25% of the population consumes  $>12\%$  of energy as omega-6 PUFA, an inverse association was found between adipose LA and acute myocardial infarction after controlling for other omega-6 PUFAs.

#### **Prospective Cohort Studies**

These observational studies use the strongest designs, minimizing both selection and recall bias. No significant associations between LA or omega-6 PUFA intake and CHD risk were seen in the Finnish Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study,<sup>40</sup> Lipid Research Clinics study,<sup>41</sup> or Honolulu Heart Program.<sup>42</sup> Modest, nonsignificant inverse associations were observed in the Multiple Risk Factor Intervention Trial,<sup>43</sup> the Irish-Boston Heart Study,<sup>44</sup> and the Health Professionals Follow-Up Study.<sup>45</sup> In the Health Professionals Follow-Up Study, CHD rates were lowest in participants with higher intake of both omega-3 and omega-6 PUFAs,<sup>46</sup> and in the Western Electric Study<sup>47</sup> and the Kupio Heart Study,<sup>48</sup> higher LA intakes or serum levels were associated with lower risk of CHD or total mortality. In the Nurses' Health Study, in which diet was assessed multiple times over 20 years,<sup>49</sup> CHD risk was  $\approx 25\%$  lower comparing the 95th and 5th percentiles of LA intake (7.0% versus 2.8% of energy, respectively). Most prospective cohort studies have not found significant associations between omega-6 fatty acid intakes and ischemic<sup>50-52</sup> or hemorrhagic<sup>50,51,53</sup> stroke or stroke mortality.<sup>54</sup> In 1 prospective study, serum

LA levels predicted lower risk of stroke, particularly ischemic stroke.<sup>55</sup> LA intakes are not associated with risk for cancer.<sup>26</sup> Therefore, observational studies generally suggest an overall modest benefit of omega-6 PUFA intake on CHD risk and no significant effect on stroke or cancer. These studies, some of which included LA intakes of up to 10% to 12% of energy, contradict the supposition that higher omega-6 PUFA intakes increase risk for CHD.

### **Omega-6 PUFA Consumption and CHD Events: Randomized Controlled Trials**

Several randomized trials have evaluated the effects of replacing saturated fatty acids with PUFAs on CHD events.<sup>56–65</sup> Intakes of PUFA (almost entirely omega-6 PUFA) ranged from 11% to 21%. In addition to the inability to double-blind these studies, many had design limitations such as small sample size ( $n=54$ ),<sup>65</sup> the provision of only  $\approx 50\%$  of meals,<sup>56</sup> outcomes composed largely of “soft” ECG end points,<sup>59,60</sup> randomization of sites rather than individuals with open enrollment and high turnover of subjects,<sup>59,60</sup> use of vegetable oils that also contained the plant omega-3 fatty acid  $\alpha$ -linolenic acid,<sup>57,59,60</sup> and simultaneous recommendations to increase fish and cod liver oil use.<sup>58</sup> Nevertheless, a meta-analysis including 6 of these trials<sup>56–60,62–64</sup> indicated that replacing saturated fatty acids with PUFAs lowered the risk for CHD events by 24%.<sup>66</sup> Of the remaining 4 studies, 1 reported a significant 45% reduction in risk,<sup>59</sup> whereas no significant effect was seen in the others.<sup>60,61,65</sup>

These trials tested the effect of replacing saturated fatty acids; no randomized trial has reported the effects of replacing carbohydrate or protein with omega-6 PUFAs on CHD risk. Although limitations are present for each trial, the combined results of these studies and the observational trials provide evidence that replacing saturated fatty acid or refined carbohydrate (eg, sugars, white bread, white rice, potatoes) with omega-6 PUFAs reduces CHD risk. On the basis of the intakes of omega-6 PUFAs used in the randomized trials, metabolic studies, and nonhuman primate studies discussed below, reductions in CHD risk might be expected with omega-6 PUFA intakes of 10% to 21% of energy compared with lower intakes, with no clinical evidence for adverse events.

### **Recommended Intakes of Omega-6 Fatty Acids**

Dietary recommendations for omega-6 PUFAs traditionally focused on the prevention of essential fatty acid deficiency but are now increasingly seeking to define “optimal” intakes to reduce risk for chronic disease, particularly CHD. The Institute of Medicine’s Food and Nutrition Board, in their Dietary Reference Intake Report for Energy and Macronutrients,<sup>67</sup> defines an adequate intake of LA as 17 g/d for men and 12 g/d for women (5% to 6% of energy) 19 to 50 years of age, approximately the current median US intake. Both the Dietary Reference Intake Report and the 2005 Dietary Guidelines for Americans<sup>68</sup> support an acceptable macronutrient distribution range (the range of intakes for a particular energy source

that is associated with reduced risk of chronic disease while providing adequate intakes of essential nutrients) of 5% to 10% dietary energy from omega-6 PUFAs. The Third Adult Treatment Panel of the National Cholesterol Education Program recommends PUFA consumption up to 10%, noting that “there are no large populations that have consumed large quantities of polyunsaturated fatty acids for long periods. Thus, high intakes have not been proven safe in large populations; this introduces a note of caution for recommending high intakes.”<sup>69</sup> On the other hand, evidence from trials in nonhuman primates has demonstrated cardiovascular benefits and no evidence of harm with LA intakes of 25% of energy for up to 5 years,<sup>70,71</sup> and randomized trials in humans have shown reduced CHD risk with omega-6 PUFA intakes of 11% to 21% of energy for up to 11 years with no evidence of harm.

Other governmental health recommendations for omega-6 fatty acid intakes (on a percent energy basis) are as follows: European Commission, 4% to 8%<sup>72</sup>; Food and Agriculture Organization/World Health Organization, 5% to 8%<sup>73</sup>; British Nutrition Foundation, 6% to 6.5% (maximum, 10%)<sup>74</sup>; the Department of Health and Ageing, Australia and New Zealand, 4% to 5% (maximum, 10%)<sup>75</sup>; and the American Dietetic Association/Dietitians of Canada, 3% to 10%.<sup>76</sup> The American Heart Association places primary emphasis on healthy eating patterns rather than on specific nutrient targets.

Advice to reduce omega-6 PUFA intakes is typically framed as a call to lower the ratio of dietary omega-6 to omega-3 PUFAs.<sup>1–4</sup> Although increasing omega-3 PUFA tissue levels does reduce the risk for CHD,<sup>77,78</sup> it does not follow that decreasing omega-6 levels will do the same. Indeed, the evidence considered here suggests that it would have the opposite effect. Higher omega-6 PUFA intakes can inhibit the conversion of  $\alpha$ -linolenic acid to eicosapentaenoic acid,<sup>79</sup> but such conversion is already quite low,<sup>80</sup> and whether additional small changes would have net effects on CHD risk after the other benefits of LA consumption are taken into account is not clear. The focus on ratios, rather than on levels of intake of each type of PUFA, has many conceptual and biological limitations.<sup>81</sup>

### **Conclusions**

This advisory was undertaken to summarize the current evidence on the consumption of omega-6 PUFAs, particularly LA, and CHD risk. 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. 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). In summary, the AHA supports an omega-6 PUFA intake of at least 5% to 10% of energy in the context of other AHA lifestyle and dietary recommendations. To reduce omega-6 PUFA intakes from their current levels would be more likely to increase than to decrease risk for CHD.

## Disclosures

## Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Ownership Interest	Consultant/Advisory Board	Other
William S. Harris	Sanford Research, University of South Dakota	Monsanto†	None	None	None	Monsanto Co,* Unilever*	None
Lawrence J. Appel	John Hopkins University	None	None	None	None	None	None
Marguerite M. Engler	University of California, San Francisco	None	None	None	None	None	None
Mary B. Engler	University of California, San Francisco	None	None	None	None	None	None
Penny Kris-Etherton	Pennsylvania State University	None	California Walnut Commission†	None	None	California Walnut Commission,* Unilever*	None
Dariusz Mozaffarian	Harvard Medical School	GSK,† Sigma-Tau,† Pronova†	None	International Life Sciences Institute,* Aramark*	None	None	None
Eric Rimm	Harvard School of Public Health	None	None	None	None	None	None
Lawrence L. Rudel	Wake Forest University School of Medicine	None	None	None	None	None	None
Frank Sacks	Harvard University/Brigham and Women's Hospital	None	None	None	None	None	None

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\*Modest.

†Significant.

## Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Scott Grundy	University of Texas Southwestern Medical Center	Donald W. Reynolds Cardiovascular Center,† Merck Project,† Abbott†	None	None	None	None	Merck,* Merck Schering Plough,* AstraZeneca,* Pfizer*	None
Ronald Kauss	Children's Hospital Oakland Research Institute	Abbott Laboratories,* Merck,* Merck/Schering-Plough*	None	None	None	None	Merck,* Pfizer*	None
Neil Stone	Northwestern University	None	None	Unilever*	None	None	Unilever*	None

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KEY WORDS: AHA Scientific Statements ■ diet ■ fatty acids ■ nutrition

**Omega-6 Fatty Acids and Risk for Cardiovascular Disease: A Science Advisory From the American Heart Association Nutrition Subcommittee of the Council on Nutrition, Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention**

William S. Harris, Dariush Mozaffarian, Eric Rimm, Penny Kris-Etherton, Lawrence L. Rudel, Lawrence J. Appel, Marguerite M. Engler, Mary B. Engler and Frank Sacks

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