

# Planning Primary Prevention of Coronary Disease

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Effective prevention of the current annual \$400 billion losses from atherosclerosis and cardiovascular disease (CVD) will require preventing primary causes rather than just decreasing signs and symptoms (risk factors) produced by those causes. All CVD risk factors predict a likelihood of CVD, but not all are causes of CVD. As a result, reducing some health risk assessment biomarkers may not appreciably reduce CVD and death. Careful review of molecular events connecting diets to death identifies two modifiable food imbalances that cause major chronic diseases in Americans. They are 1) imbalance between ingestion and expenditure of food energy, and 2) imbalance between omega-3 and omega-6 essential fatty acid levels in ingested foods. Health insurers could reduce costs and revolutionize preventive health care by monitoring omega-3 and omega-6 proportions in blood fatty acids and by using personalized interactive food choice software to adjust food intakes to fit individual preferences.

## Introduction

The United States Centers for Disease Control and Prevention describe cardiovascular disease (CVD) as a preventable condition, but economic losses in the United States caused by CVD remain near \$400 billion annually [1]. Death rates of CVD have decreased since 1980 but the incidence and prevalence of CVD are constant or rising [2]. Readers may wonder what continues causing 1.2 million Americans to have a heart attack each year and why one in three adults die with some form of CVD if this condition is preventable. The dissonance increases when realizing that the United States spends the most money of any nation on health care costs per person.

Much of the loss likely comes from misunderstanding and neglecting two clinical maxims: 1) a biomarker that associates with disease can predict risk but the association

does not prove that it causes the risk; and 2) treatments that decrease an associated biomarker (risk factor) will not necessarily decrease the cause of the disease. Effective use of health care funds and prevention of societal loss from CVD will require recognizing and modifying those risk factors and biomarkers that mediate CVD processes rather than those that are merely associative consequences of primary CVD causes. Smoke is a useful marker for predicting risk of fire, but it is not the cause of the fire.

Health care developed and promoted by treatment-oriented clinicians, drug companies, and hospitals focuses (quite profitably) on treating the signs and symptoms that predict and define CVD. However, readers may wonder who is focusing on preventing the factors that cause those signs and symptoms. Current health risk assessments (HRA) often measure surrogate biomarkers that replace actual clinical end points and they may be used beyond their valid limits [3]. Attempting to stop fires by waving away smoke is futile.

The public needs more open discussion and accountability for the logic that identifies molecular events connecting causes with their consequences so it can redirect resources toward known tools and valid targets for intervention [4,5••]. The medical care system offers oversimplified information about surrogates that it treats while important unacknowledged factors that cause disease risk continue unchanged. The situation allows yet another generation to develop signs of disease that will eventually be treated but not prevented.

## An Irrational Surrogate End Point

Imprecise logic in handling information about the associative CVD risk factor, blood cholesterol, was reviewed by comparing two questionnaires [5••]. A 1978 European questionnaire used two items: 1) “Do you think there is a connection between plasma cholesterol level and the development of coronary heart disease?” (189 yes; 2 no); and 2) “Do you think that our knowledge about diet and coronary heart disease is sufficient to recommend a moderate change in the diet for the population in an affluent society?” (176 yes; 16 no). Clearly, the experts recognized the association of diet and disease, although details of fatal causal connections or desired corrective changes in diet were not specified.

At that time, some American scientists and drug companies wished to develop and market “anticholesterol” drugs following two large and expensive CVD initiatives that had little success [5••]. The situation recalled by Steinberg [6] was that “The National Institutes of Health (NIH) realized that launching a national program to treat high blood cholesterol levels would be enormously complex and expensive. They could not justify that expense without first having iron-clad proof that treatment would work”. In contrast to the rigorous scientific process of intentionally designing tests to disprove a hypothesis, disproving the hypothesis for a large clinical trial involving thousands of people has embarrassing consequences [5••].

Accordingly, Steinberg chaired a 1984 NIH Consensus Development Panel that voted on two questions with logic very different from the European questionnaire: 1) “Is the relationship between blood cholesterol levels and coronary heart disease causal?” (14 yes; 0 no); and 2) “Should an attempt be made to reduce blood cholesterol levels of the general population?” (14 yes; 0 no). Although a vote does not constitute scientific proof, this 1984 consensus was influential in the US Food and Drug Administration’s decision to justify approval of cholesterol-lowering therapy without requiring manufacturers to submit at the time of application clinical trial data demonstrating efficacy in lowering serious CVD events [6]. Many panel members (like their European colleagues) regarded CVD as a diet-induced disease caused by imbalanced food energy. Their report urged that the first step in treatment should be caloric restriction and weight loss, and that “even when use of drugs seems appropriate, it is important to stress that maximal diet therapy should be continued” [7].

Specific details of diet-caused fatal processes and of the desired diet therapy were not clearly indicated by the 1984 panel. Rather, development of dietary advice was delegated to NIH staff in a newly formed National Cholesterol Education Program. Today (25 years later), we see aggressive marketing of cholesterol-lowering agents and continued misunderstanding of how food choices cause disease and death [5••]. The present review examines known biochemical steps that connect food to CVD and death in an attempt to redirect attention and resources toward rational causal targets and toward tools for effective primary preventive interventions that could lower the need for treatments.

## How Food Hurts

Two general food imbalances cause major chronic diseases [5••]. One is imbalance between rates of intake and expenditure of food energy (Fig. 1). The primary cause for an individual’s rate of food energy intake is a network of appetitive neurotransmitters that regulate the sense of hunger and satiety. Appetite responds to the protein, carbohydrate, or fat content of food differently in different people [5••]. We convert food to acetyl-coenzyme A

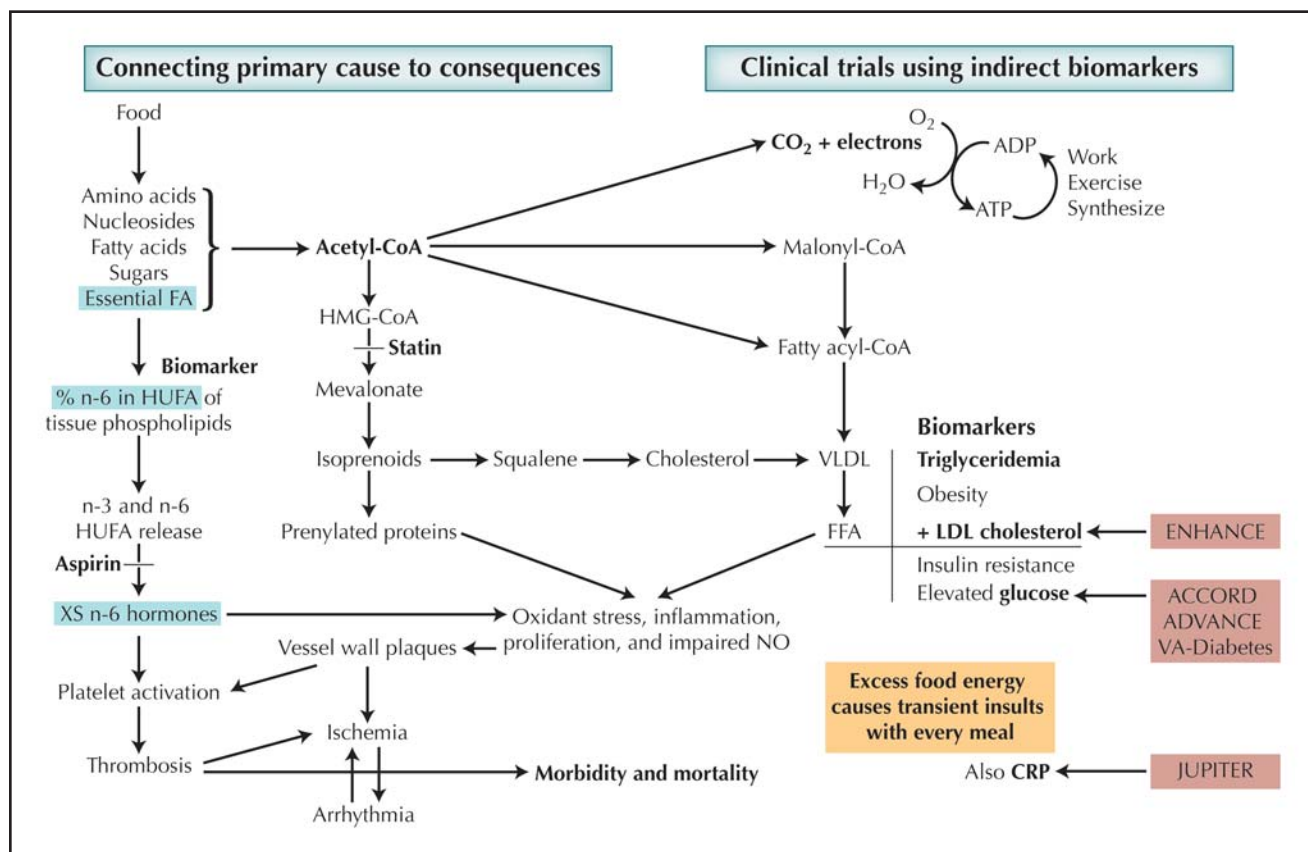
(acetyl-CoA), and with enough exercise convert it to CO<sub>2</sub>. However, a big meal gives more food energy than we expend in the next hour. As a result, excess acetyl-CoA from metabolism of fats, sugars, and amino acids forms fatty acids and triglycerides that enter the blood stream as very low-density lipoproteins (VLDL).

Lipoproteins are steadily hydrolyzed in the blood to form free fatty acids (FFAs) that irritate blood vessels, causing inflammatory oxidant stress [4], elevated C-reactive protein (CRP) levels, insulin resistance, type 2 diabetes, and obesity (sometimes discussed as part of a “metabolic syndrome”). We need stronger proof of whether these FFA-induced biomarkers actually cause CVD and whether lowering them will effectively lower fatal CVD events. Low-density lipoprotein (LDL) cholesterol is formed whenever circulating VLDL releases large amounts of FFAs. These variables are interdependent and inseparable in clinical conditions (although separable in careful in vitro laboratory studies). Readers may wonder why FFA-induced events are not attended to as vigorously as the LDL cholesterol that is formed while FFAs are released.

Excess acetyl-CoA after a big meal also forms more 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA), which goes on to make mevalonate, isoprenoids, and prenylated regulatory proteins [8••,9]. These regulators may amplify inflammatory oxidant stress triggered by FFAs [10,11], converting transient postprandial insults into chronic blood vessel injuries that promote thrombosis, ischemia, and death (Fig. 1) [4]. Amplification of frequent postprandial insults into chronic injuries is a serious problem because vascular damage accumulates from childhood onward [12]. Prevention of CVD should begin in childhood and continue for life. Statin drugs slow the rate of mevalonate formation and may lower some amplified inflammatory insults following every big meal. Alternatively, amplification of transient insults can be less whenever tissue 20- and 22-carbon highly unsaturated fatty acids (HUFA) contain more omega-3 (n-3) than omega-6 (n-6) HUFA [4,5••].

Impacts of proportions of n-3 and n-6 acids are illustrated in Figure 1. Heart attacks kill people by thrombosis, ischemia, and arrhythmia. Those processes are mediated by activated platelets and blood vessel plaques and amplified by excessive n-6 eicosanoid hormone actions. Such actions happen more when n-6 exceeds n-3 in HUFA, an imbalance caused when food choices have imbalanced amounts of n-6 and n-3 fats. Thus, the proportion of n-6 in the HUFA in our tissues is predicted from fatty acids in foods typically eaten [13].

The proportion also predicts the likelihood of harmful CVD events [13,14]. As a result, the percent of n-6 in HUFA is a valid surrogate endpoint for monitoring dietary interventions to prevent CVD [3]. In contrast, many clinical trials study other biomarkers associated with morbidity and mortality (Fig. 1). Readers may wonder what caused so much attention on treatments to decrease levels of secondary biomarkers such LDL cholesterol, obesity, glucose, and CRP rather than on primary prevention



**Figure 1.** Connections by which food choice causes consequences. The left side shows how imbalances in dietary omega-3 (n-3) and omega-6 (n-6) connect to the % n-6 in HUFA, a tissue biomarker causing cardiovascular disease morbidity and mortality. The middle of the figure shows how food energy density causes transient postprandial inflammatory events. The right side names recent clinical trials that raise questions of whether blood LDL cholesterol and glucose actually mediate fatal inflammation-induced thrombotic, ischemic, and arrhythmic cardiovascular disease events. ACCORD—Action to Control Cardiovascular Risk in Diabetes; ADP—adenosine diphosphate; ADVANCE—Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; ATP—adenosine triphosphate; CRP—C-reactive protein; ENHANCE—Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression; FA—fatty acid; FFA—free fatty acid; HMG-CoA—3-hydroxy-3-methylglutaryl coenzyme A; HUFA—highly unsaturated fatty acid; JUPITER—Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; LDL—low-density lipoprotein; NO—nitric oxide; VA—Veterans Affairs; VLDL—very low-density lipoprotein; XS—excess.

of dietary imbalances that cause increased levels of such biomarkers. Understanding molecular events connecting cause to consequence helps readers make valid inferences about useful targets for intervention (Fig. 1). Successful primary prevention could focus on eating more n-3 fats, fewer n-6 fats, and fewer calories per meal.

### Considering Risk Factors

The American Heart Association 2009 report notes that the CVD burden remains high and that control of risk factors remains an issue [2]. It lists 57 factors associated in diverse ways with CVD risk. The report notes that “dietary habits affect a broad range of established and novel risk factors” and asserts that “randomized clinical trials and prospective observational studies can better quantify the effect of dietary habits on clinical outcomes.” However, “diet advice” from clinicians in controlled clinical trials proved no better than no advice at all [15]. Ironically, treatment with n-3 fatty acid capsules gave better results than statin pills but was not considered “dietary”.

The pharmacokinetics of absorption, distribution, and fate of ingested nutrients requires recognizing the rates by which nutrients convert into diverse metabolites, hormones, and receptor-mediated actions, all of which have complex pharmacodynamics in their onset, rate, and duration. Interactions among these diet-driven features are not as simple as those in testing therapeutic drugs. Results from recent clinical trials remind us to avoid oversimplifying how various surrogate biomarkers (risk factors) become elevated and how specific interventions may modify them [16]. Whatever surrogate improvement is targeted, net clinical benefit will still depend on clinical events averted and lives improved.

The pharmacodynamics of food in hurting health is mostly neglected in food marketing messages. Countries that once had diets described as “traditional Mediterranean diet” (associated with low CVD prevalence) now have a higher prevalence of myocardial infarction [17], as diets change with food marketing priorities and misunderstandings about “healthy” eating habits. Readers might wonder what organization in a market society could maintain

financial stability while providing positive health pressures to counter-balance unhealthy (but profitable) marketing pressures. Such an organization could help the public learn how food hurts and how to prevent easily modified causes of CVD and their multibillion dollar losses.

The scientific literature is filled with controlled experiments that test hypotheses about connections between cause and consequence. Each tightly controlled test of a hypothesis has little public visibility but it serves as a valuable part of the cumulative evidence (over 18 million reports are in the National Library of Medicine PubMed system). Expensive large clinical trials do not test each detail but should be designed and interpreted using these bits of evidence. This is especially true for rates of formation and action of FFAs and n-6 eicosanoids in converting transient postprandial insults into chronic injuries.

While scientists revise and refine a specific hypothesis, the broader scientific community may suspend disbelief until all related evidence is interpreted consistently. In this situation, dissonance can develop as advocates and marketers aggressively inform the public about one aspect while ignoring others. The conceptual network sustaining the “lipid hypothesis” that claims elevated blood cholesterol causes death still has imprecise concepts, surrogates, and definitions that will yield eventually to precise logic and evidence in open scientific dialog [5••]. Recent evidence from the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial [18] caused the mass media to openly question whether the CVD-associated biomarker, elevated LDL cholesterol, is caused by factors that also cause CVD and whether cholesterol drugs actually do any good [19••,20].

Cardiovascular harm from food energy may be more in the rate (intensity) of food energy influx per hour (energy density) than in overall calories accumulated per week. Healthy weight maintenance will not reflect transient postprandial insults that can be amplified by actions of prenylated proteins and n-6 eicosanoids (Fig. 1). Obesity markers (body mass index, waist/height ratios, body mass) divert attention from the transient rates by which energy density elevates FFA levels in blood and causes harmful outcomes. Similar attention to another CVD-associated biomarker, elevated blood glucose, led to the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and the VA-Diabetes trial [21], all of which showed the failure of lowering blood glucose to lower CVD death. Tactics for lowering blood glucose may not lower the postprandial FFA (Fig. 1) that causes insulin resistance and elevated glucose while also causing the vascular insults leading to CVD.

Early termination of Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) [22] in 2008 came with evidence that rosuvastatin lowered levels of CRP, which is an acute stress protein associated with inflammatory conditions.

With lowered levels of both LDL cholesterol and CRP, the study widens public questioning of whether LDL cholesterol or inflammation is the real cause of CVD deaths [23]. In this regard, anti-inflammatory actions of tissue n-3 HUFA are also associated with reduced levels of CRP [24]. Thus, results from the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Heart Failure (GISSI-HF) trial [25,26] comparing n-3 HUFA and rosuvastatin point again to more benefit from n-3 HUFA than statins [15]. Readers may wonder what has kept public attention away from known inflammatory, thrombotic, and arrhythmic aspects of n-6 HUFA for so long [5••,27]. For those who want scientists to carefully and skeptically test hypotheses about preventing CVD, 2008 was a watershed year.

### Cholesterol or Inflammatory Mediators?

The word “cholesterol” has been used to allude to many health aspects over the years, as has the imprecise word “inflammation.” The oxidative, phagocytic actions of innate immune cells such as macrophages and neutrophils include release of signaling mediators that create an inflammatory region as they kill and ingest nearby cells. Activated phagocytic cells accumulate indigestible cholesterol from damaged cell membranes and lipoproteins, sometimes forming cholesterol crystals that are an historic characteristic feature of inflammatory vascular plaques [5••]. In a sense, accumulated cholesterol in macrophages is to inflammation like smoke is to fire, an associated but not causal feature. Readers may wonder why more attention has not focused on preventing the inflammatory conditions that cause cholesterol accumulation in vessel walls.

Circulating lipoproteins carry cholesterol that usually does not accumulate much in vessel walls in the absence of inflammatory events. Although blood cholesterol is a much-discussed risk factor for predicting CVD in the United States, it has an inverse association in Japan, where the highest mortality rate was for men with less than 160 mg/dL and the lowest rate was for men with more than 250 mg/dL [28]. A 25-year follow-up study of cohorts in the Seven Countries Study [29] also noted that absolute levels of circulating blood cholesterol were poor predictors of absolute risk of CVD mortality, especially in Japan. Review of those results suggested that elevations of blood cholesterol induced by food energy flux may be fatal only insofar as people have inflammatory states from less n-3 than n-6 in their tissue HUFA [5••].

One might hypothesize more harm from imbalanced n-3 and n-6 HUFA than from imbalanced intake and expenditure of energy. Figure 1 illustrates how imbalanced tissue HUFA can cause excessive n-6 eicosanoid signaling that amplifies transient postprandial inflammation into fatal consequences. This chain of events brings attention to the likely benefits of eating foods that prevent deficits of n-3 in tissue HUFA and thereby prevent the inflammatory, thrombotic, and arrhythmic

aspects of CVD. Important proof of harm mediated by transient n-6 eicosanoid actions comes from physiologic and pharmacologic laboratory studies rather than long-term clinical trials.

Efforts to describe and predict the quantitative impact of dietary polyunsaturated fatty acids on proportions of n-3 and n-6 in tissue HUFA led to an empirical competitive hyperbolic relationship (<http://efaeducation.nih.gov/sig/hufacalc.html>) [13] that predicted observed proportions in HUFA for individuals with a wide range of voluntary dietary intakes [30]. Populations with more n-6 than n-3 in plasma HUFA (Table 1) have higher CVD mortality rates than those with less than half n-6 [14]. In this sense, people who have less than half of their HUFA as n-3 acids have an n-3 deficit. Different formats of the same analytical data describe HRA status (Table 1) with the percent n-3 in HUFA ranging from 13% to 68% whereas the sum (eicosapentaenoic acid [EPA] + docosahexaenoic acid [DHA]) ranges from 1.6% to 12.8% [5••].

Recent evaluation of effective ways to quantitate n-3 status showed the utility of testing whole blood and expressing gas chromatographic results as the percent n-3 in HUFA [31•]. As most tissue HUFAs are either n-3 or n-6 acids, this value equals 100 minus percent n-6 in HUFA. [5••]. Tests for n-3 or n-6 status are economically arranged in a low-cost, high-throughput manner by using a 50- $\mu$ L fingertip blood sample [32] spotted on paper [33] and converted rapidly to methyl esters using a microwave [34••]. Other ways of optimizing tests are described by Masood and Salem [35], as investigators recognize the importance of monitoring individual HUFA status in large clinical studies. Using streamlined procedures in a high-throughput facility will likely drop the cost per HUFA test to less than 10% of that for current research-oriented tests.

For many years, scientific reports consistently associated seafood intake with fewer CVD events. Understanding underlying molecular processes for this protection steadily improved during the 1970s and 1980s as HUFA-derived eicosanoid mediators of immune/inflammatory, thrombotic, and arrhythmic events were discovered. Their importance in mediating physiology of nearly every tissue of the body was recognized in 1983 with the Nobel Award in Medicine and Physiology. A greater ability of the n-6 leukotriene B4 (compared with the n-3 leukotriene B5) to attract phagocytic leukocytes and amplify inflammatory conditions alerted scientists to serious chronic inflammatory consequences from ill-informed food choices [36]. Recently, different intensities of n-3 and n-6 actions were seen in an elegant study that presented multiple instances wherein n-6-mediated events were more potent or vigorous than corresponding n-3-mediated events [37••]. In the past 30 years, many detailed controlled experiments confirmed excessive n-6 HUFA actions that can be moderated either by patented therapeutic agents or by increasing tissue proportions of competing n-3 HUFA.

Higher fish consumption was associated with slower progression of coronary atherosclerosis in women with CVD [38]. Six large clinical studies involving over 2 million person-years of follow-up were reviewed recently [39]; all confirmed that CVD clinical events were less with higher seafood intake. Also, there were fewer brain abnormalities in older adults who consumed tuna or other fish three or more times per week compared with those eating less than once per month [40]. Fried fish intake was not correlated with lower CVD, supporting the concept that a higher dietary intake of n-3 HUFA prevented CVD events. In keeping with accumulated evidence from such results, the American Heart Association has strengthened its advice to consume fish, especially oily fish, at least twice a week [41•].

### A Rational Surrogate End Point

This evidence depended on self-reported food intake and on validity of the estimated content of n-3 HUFA in the food eaten. Both measures have appreciable uncertainty. Whereas preventive medicine must focus on the primary causal imbalance of n-3 and n-6 fats in foods ingested, more valuable evidence of intakes will come from measuring the actual n-3 status in tissues of an individual. Blood tests in large clinical trials will confirm that the percent n-3 in HUFA is a valid surrogate in the connected pathway between diet and death (Fig. 1). Such test results can also confirm an individual's compliance with personalized preventive nutrition advice. Thus, tests are a valuable tool in motivating individuals to alter their personal food selections [42].

Developing quantitative relationships between dietary n-3 and n-6 fats and the proportions of n-3 and n-6 in tissue HUFA was limited initially by a subject population with a narrow range of food choices that gave an average 75% n-6 in HUFA [13]. The empirical relationship was later strengthened with data from a larger sample of people with a wider range of voluntary intakes [30]. Applying that relationship to multiple 24-hour recall data of 6258 people in the Multiple Risk Factor Intervention Trial (MRFIT) study predicted that quintiles of n-3 HUFA intake would have these values for the percent n-6 in HUFA of blood: 83%, 82%, 81%, 77%, and 62%, which were associated with 42, 39, 35, 35, and 24 deaths, respectively [14]. These values agree with data for ethnic subsets of Canadians, which ranged from 78% to 38% n-6 in HUFA, with mortality rates varying proportionately [14]. Many populations seem to be unknowingly practicing primary prevention of CVD.

A treatment-oriented comment from a noted cardiologist suggested that since we now have a treatment and a blood test, people might soon brag about their own personal n-3 status number [42]. Readers may recognize that nutrients effective for secondary prevention treatments will likely also work in a primary prevention regimen. Systematic HRA monitoring of the percent n-3 in HUFA of individuals will give stronger evidence of benefit and stronger motivation for preventing primary imbalances.

**Table 1. Diversity in the proportions of omega-3 and omega-6 fatty acids**

Population	Gas chromatography analysis values										Health risk assessment values			
	Sat	Mono	18:2n-6	18:3n-3	20:3n-6	20:4n-6	20:5n-3	22:5n-3	22:6n-3	HUFA	% n-6 in HUFA	% n-3 in HUFA	EPA + DHA	
Greenland	43.6	19.2	14.0	0.1	1.2	5.2	4.9	1.6	7.9	21	32	68	12.8	
Japan, 57-year old	47.6	13.6	17.3	0.2	-	6.4	3.7	1.2	7.3	19	34	66	11.0	
Quebec Inuit	-	-	22.2	0.0	-	6.2	3.0	-	5.0	14	44	56	8.0	
Japan	30.4	21.3	31.7	0.2	1.0	6.6	2.6	0.7	5.4	16	47	53	8.0	
Japanese dietitians	32.1	21.0	27.8	0.9	0.7	4.9	1.7	0.4	3.2	11	51	49	4.9	
England	30.7	20.1	33.3	0.8	1.7	7.2	1.5	1.2	3.0	15	62	38	4.5	
Minnesota	40.9	12.3	21.6	0.2	-	12.2	0.7	1.0	4.5	18	66	34	5.2	
Spain	47.1	19.7	15.9	0.1	2.2	6.8	0.6	0.4	5.5	23	72	28	6.1	
James Bay	-	-	21.1	0.0	-	9.3	0.7	-	3.0	13	71	29	3.7	
Quebec urban	-	-	22.1	0.0	-	6.4	0.5	-	1.3	8	78	22	1.8	
ARIC study	49.3	9.2	22.0	0.1	-	11.5	0.6	-	2.9	15	77	23	3.4	
Detroit, 25-year old	31.1	24.1	26.5	0.4	1.5	7.6	0.2	0.3	1.8	12	82	18	1.9	
Ohio	45.0	15.0	25.7	0.6	1.1	10.2	0.7	0.2	0.8	13	87	13	1.6	

n-3—omega-3; n-6—omega 6; ARIC—Atherosclerosis Risk in Communities; DHA—docosahexaenoic acid; EPA—eicosapentaenoic acid; HUFA—highly unsaturated fatty acid; mono—monounsaturated fat; sat—saturated fat.  
 (Adapted from Lands [5••].)

Recently, only 4% of Midwestern patients with acute coronary syndrome had erythrocyte n-3 HUFA levels regarded as near a “desirable” range (> 8% EPA + DHA) [43]. The results confirm an earlier report of people with third quartile n-3 HUFA (about 5.0%) having 70% lower risk of primary cardiac arrest than those with the lowest quartile (about 3.3%) [44].

A recent prospective cohort study of 228 postmenopausal women described that higher levels of 22:6n-3, a biomarker of n-3 status, were associated with slower progression of coronary atherosclerosis [45]. Similarly, whole blood levels of EPA + DHA were lower in middle-aged patients with acute coronary syndrome than in controls (1.7% vs 2.4%) [46]. Furthermore, of 265 patients hospitalized with their first myocardial infarction, 10 cases of ventricular fibrillation during the initial 6 hours had a lower content of EPA + DHA (4.9%) than 185 controls (6.1%) [47].

Dietary n-3 and n-6 fatty acids compete in the desaturation, elongation, acyltransferase, and hydrolysis events that maintain tissue HUFA levels [5••]. The competitive metabolism is more visible when dietary supplies of n-3 and n-6 are similar and near 1% of food energy, but it is always present [48]. Current intakes of the n-6 linoleate in United States are much higher now than a century ago, and a controlled experiment showed that an accumulated n-3 HUFA, eicosapentaenoic acid (20:5n-3), was lower when dietary linoleate was 10.5% of food energy rather than 3.8% [49]. The result illustrates the merits of direct HRA monitoring of tissue status rather than attempting to manage uncertainties about competing interactions among nutrients.

As with CVD, considerable epidemiologic evidence on mood disorders also supports a protective effect of eating n-3 HUFA. The Omega-3 Fatty Acid Subcommittee of the Committee on Research on Psychiatric Treatments of the American Psychiatric Association reported a meta-analysis of randomized controlled trials showing benefits of n-3 HUFA intake in moderating unipolar and bipolar depression [50]. As a result, they recommend that all adults should eat fish two times per week, and patients with mood, impulse-control, or psychotic disorders should consume 1 g/d of EPA + DHA. Lower biomarker levels in acute coronary syndrome patients with depression (2.9%) than without depression (3.3%) fits the hypothesis that an n-3 deficit may be a common underlying causal mediator [51]. Other evidence that is beyond the scope of this short review suggests that primary prevention of an n-3 deficit in HUFA could lower financial losses from atherosclerosis, heart attacks, psychiatric disorders, unproductive workplace behaviors, immune-inflammatory disorders, cancer progression, and length of stay in hospitals.

## Conclusions

The \$400 billion lost to CVD now flows to those paid to treat and correct CVD problems rather than those who prevent the need to treat them. In a market economy, public information and education comes from marketing messages

of competing firms. Aggressive marketing of profitable treatments supports public education favoring continued treatments. However, lowering noncausal risk factors is not an effective expenditure for preventing future health care expenditures. Clinical descriptions of disease differ from biochemical understandings of disease mechanisms. Accountable prevention of losses from CVD needs some marketer to profit when preventing the need for expensive health care services. Citizens and employers who pay health insurer actuaries to manage health treatment costs should urge redirecting efforts and resources toward known tools [5••] for primary prevention (eg, increasing n-3, decreasing n-6 and calories per meal) to lower future financial losses and gain savings for society.

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## Disclosure

Dr. Lands serves as a member of the Board of Directors of Omega Protein, Inc. and also owns stock in the company.

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