

Diets and Clinical Coronary Events The Truth Is Out There

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Perhaps no question is asked more often of physicians, and particularly of cardiologists, than, "What should I be eating to prevent heart disease?" Over recent years, vast amounts of literature have been produced on this topic, and fortunes have been made from books offering advice and programs offering supervision. Even one of the most respected nutritional epidemiologists has written a lay-press book, recognizing the critical need for improved dietary habits in the general population.¹

Despite the glut of dietary advice, however, the direction that Americans are taking is discouragingly clear. Although lipid levels and the age-adjusted incidence of coronary artery disease (CAD) are declining gradually, rates of obesity and diabetes (two risk factors for CAD) are skyrocketing,² threatening a reversal of the gains achieved to date.

Information about the "best diet" is incomplete, unscientific, and often conflicting. On one hand, people wishing to avoid CAD or prevent its progression are told to eat less fat. Some undoubtedly interpret this as a recommendation to eat a high-carbohydrate diet instead, contributing to epidemics in diabetes and obesity, and placing them at risk for CAD. On the other hand, many overweight or obese Americans attempt to lose weight through one of the popular weight-reducing diets, many of which severely restrict carbohydrates. The resulting increase in proportional calories from protein (and fat) may pose a risk; a recent Science Advisory from the American Heart Association has expressed concern about weight-loss diets recommending a high proportion of calories from protein.³ According to the Advisory, the possible risks of such diets include metabolically induced liver and kidney damage and CAD. Unfortunately, very little in this public health warning can be substantiated by clinical outcome studies.

Thus, people with and without CAD, and their doctors, still face a dilemma. Fats are considered "bad" because they lead to cardiovascular events. However, one of the alternative energy sources, carbohydrates, is "bad" because it increases the risk of diabetes, and the other, protein, is "bad" because of increased burdens on the liver and kidneys. What, then, can be done to give patients a simple answer to their most frequent question: "What can I eat that will keep me from dying, having a heart attack, or having a stroke?"

Current State of Evidence

Supplying the Essentials

Besides water, the human body requires various nutrients for proper function (Table). A balanced diet is one that meets the requirements of essential nutrients. For vitamins and minerals, the requirements are fairly straightforward: The US government has set minimum daily requirements for their intake because each such nutrient is required and one cannot do the job of another. Certain amino acids and fatty acids also are considered essential, but the optimum mix of energy sources, to prevent CAD or enhance health in other ways, is unknown.

Humans have three sources of energy, each of which comes in a specific form: carbohydrates, proteins, or fats. The US Departments of Agriculture and Health and Human Services jointly developed the Food Guide Pyramid, which recommends servings from various food classes (Figure 1).⁴ These recommendations call for 55% to 60% of daily calories from carbohydrates, 10% to 15% from protein, and <30% from fat.

Since 1994, food products regulated by the US Food and Drug Administration (FDA) have been required to carry a Nutrition Facts Label (Figure 2) to help consumers in their efforts to improve nutrition. Each label shows the "% Daily Value" (%DV) for several nutrients. To calculate the %DV for vitamins and minerals, the FDA uses Reference Daily Intakes (RDIs), based on Recommended Dietary Allowances (RDAs) set by the Food and Nutrition Board (FNB) of the National Academy of Sciences. For nutrients without set standards, such as carbohydrates, protein, fat, and fiber, the FDA uses Daily Reference Values (DRVs), which are calculated as the proportion of calories that these nutrients should represent in a 2000-calorie reference diet, based on the Food Guide Pyramid recommendations.

The RDAs originally focused on prevention of classic nutritional deficiency diseases, such as rickets, but they have expanded to include the "reduction of risk of chronic diseases such as osteoporosis, cancer, and cardiovascular disease."⁵ Therefore, the FNB, with Canadian health authorities, has been developing new methods for setting nutritional reference values. These so-called Dietary Reference Intakes (DRIs) will reflect extensive literature reviews, consensus

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Essential Nutrients for Human Health

Category	Essential Nutrients
Source of energy (macronutrients)	Carbohydrates, fats, proteins
Vitamins	A, B ₁ (thiamine), B ₂ (riboflavin), B ₃ (niacin), B ₅ (pantothenic acid), B ₆ (pyridoxine), B ₇ (biotin), B ₉ (folic acid), B ₁₂ (cyanocobalamin), C (ascorbic acid), D, E, K
Minerals	Calcium, phosphorus, magnesium, iron
Trace minerals	Zinc, copper, manganese, iodine, selenium, molybdenum, chromium
Electrolytes	Sodium, potassium, chloride
Amino acids	Histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, valine
Essential fatty acids	Linoleic, α -linolenic

recommendations, and input from federal agencies, industry, academia, public interest and professional groups, and others. Unfortunately, the literature too often lacks outcomes data from adequately controlled trials.⁶

Epidemiological Studies

The diet-heart health movement began with seminal epidemiological observations. In 1970, the classic Seven Countries study showed a direct correlation between dietary fat and total cholesterol levels and between total cholesterol levels and coronary-related mortality.⁷ Multiple other studies reported similar relations, including lower rates of coronary deaths in China (compared with the United States), where the diet is typically low in fat but high in fiber intake.⁸⁻¹⁰

In studies conducted over 20 years, however, the Harvard School of Public Health showed that total fat intake bore no

significant relation to CAD risk. In fact, their Nurses' Health Study and other studies of almost 300 000 Americans showed that some fats, such as olive oil and other monounsaturated fats, can reduce the risk of CAD.¹¹⁻¹³ Moreover, saturated fats, which should represent the smallest proportion of daily calories according to the Food Pyramid, appear to carry little more risk than carbohydrates, the food class representing the bulk of recommended calories. In addition, the fat contained in margarine (trans-fatty acids) appears harmful, which has particular relevance given that Americans have been told to use margarine instead of butter. Four other epidemiological studies^{14,15} have shown no evidence that men who eat less fat live longer or have fewer myocardial infarctions (MIs).

Epidemiological studies are important because they can generate hypotheses, but they cannot determine causality. A correlation between a risk factor (diet) and an outcome (CAD

Food Guide Pyramid

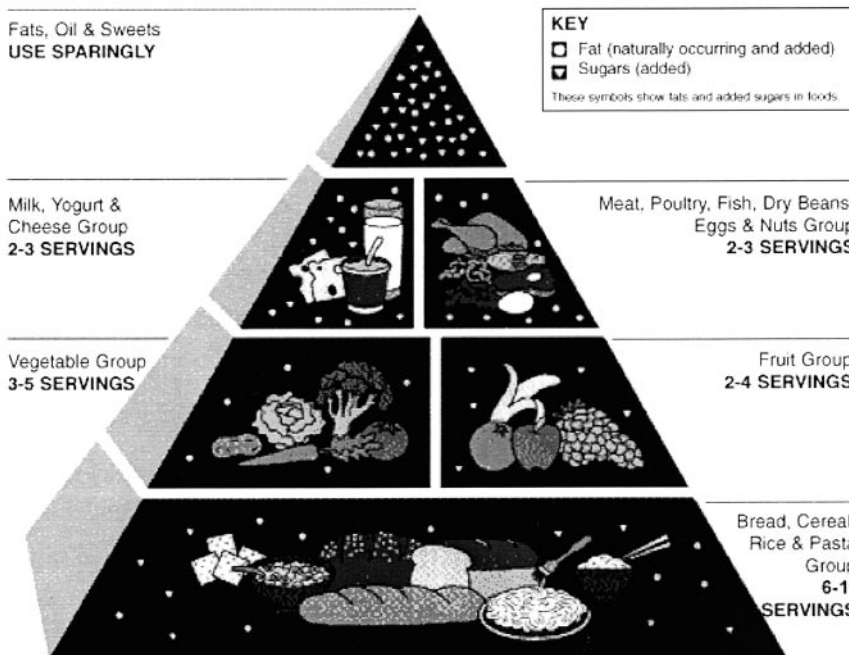


Figure 1. The US Food Guide Pyramid.⁴

Nutrition Facts	
Serving Size 1 cup (236ml)	
Servings Per Container 1	
Amount Per Serving	
Calories 120	Calories from Fat 45
% Daily Value*	
Total Fat 5g	8%
Saturated Fat 3g	15%
Cholesterol 20mg	7%
Sodium 120mg	5%
Total Carbohydrate 11g	4%
Dietary Fiber 0g	0%
Sugars 11g	
Protein 9g	17%
Vitamin A 10%	Vitamin C 4%
Calcium 30%	Iron 0% • Vitamin D 25%
*Percent Daily Values are based on a 2,000 calorie diet. Your daily values may be higher or lower depending on your calorie needs.	

Figure 2. A typical US Nutrition Facts Label.

events) does not prove cause and effect but rather provides a plausible theory to test in a trial. Furthermore, general relations cannot be used to draw conclusions about specific diets. For example, epidemiological evidence that fats are harmful when consumed in a mixed diet does not necessarily mean that fats are harmful when consumed in a carbohydrate-restricted diet.^{16,17}

Biological Surrogate Data

Because of the widespread belief that outcomes studies are not feasible for dietary interventions, the field has been dominated by small studies measuring intermediary end points. Although these studies have built a huge knowledge base about the short-term metabolic effects of dietary interventions, they provide little direct evidence about which diets can prolong life or prevent CAD events.

These studies also suffer from a major design flaw that only recently has been accepted in cardiovascular medicine: Biochemical measures can provide mechanistic insights and are essential building blocks in therapeutic development but cannot reliably predict the effect of proposed interventions on clinical events. A classic example is the Cardiac Arrhythmia Suppression Trial (CAST), which tested the theory that suppression of ventricular ectopy after MI reduces sudden deaths.¹⁸ The study randomized patients with ventricular arrhythmias that could be suppressed with encainide, flecainide, or moricizine to receive active drug or placebo. The groups given the effective antiarrhythmic agents had higher mortality rates than those given placebo, primarily from arrhythmia or cardiogenic shock.

Hormone-replacement therapy provides another example of this phenomenon. In this case, salutary effects of therapy on low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol did not translate into clinical benefit.¹⁹ Clearly, the effect of an intervention on one putative surrogate measure does not tell the whole story; this lesson is as likely to pertain to food as to drugs. Indeed, a recent National Institutes of Health (NIH) meeting concluded that the term "surrogate" is rarely appropriate because of the stringent criteria that must be met to prove reliability of a proposed

measure.²⁰ Diet recommendations should conform to the same levels of evidence as for other therapies—that is, measuring the effects of dietary approaches on how people feel and on fatal or disabling events.

Behavioral Data

Surprisingly little information is available to address whether diet composition can affect appetite or quality of life. The field has been driven partly by the knowledge that fat has 9 kcal/g, whereas carbohydrates and protein have only 4 kcal/g. Thus, a quantity of food as carbohydrate or protein logically would add less to body weight compared with the same quantity as fat. Many popular diets, however, are built on the concept that fat suppresses appetite, leading to consumption of fewer calories, although evidence from high-quality studies is lacking. In fact, fat appears to be less satiating than either protein or fiber-rich carbohydrates.²¹

Angiographic Data

Few randomized, controlled trials have investigated dietary interventions alone to arrest the progression of CAD. The Lifestyle Heart Trial randomly allocated 48 patients to either a very low-fat diet (10% of daily energy intake) plus intensive lifestyle intervention (exercise, stress management, smoking cessation, group counseling) or usual care.²² After 1 year, the experimental group showed more favorable changes in angina frequency and angiographic stenosis. After 5 years, the experimental group patients still had more favorable changes in coronary stenoses and fewer cardiac events but did not have lower mortality.²³ Limitations to this study include restrictive exclusion criteria, multiple confounding interventions in the experimental group, and disclosure of group assignment to potential subjects before obtaining their consent to participate.

In the St Thomas Atherosclerosis Regression Study (STARS), 90 men were randomized to one of three arms: usual care; a low-fat, low-cholesterol diet, high in omega-6 and omega-3 fatty acids and fiber; or this diet plus cholestyramine.²⁴ After 3 years, patients in the diet-only group had significant improvements in several angiographic variables and fewer cardiac events or interventions compared with the usual-care group, but mortality rates were similar.

Randomized Outcomes Studies

Low-Fat Diets

Studies that have assessed the effects of changing the type and amount of fat in the diet offer few definitive conclusions. The Cochrane Collaboration recently released a meta-analysis of 27 randomized intervention trials (total of 40 intervention arms) lasting ≥ 6 months. No significant effect was shown with reduced or modified dietary fat on overall mortality, cardiovascular mortality, or cardiovascular events after sensitivity analysis (Figure 3).²⁵ The investigators did note significant reductions in cardiovascular events and in total mortality among high-risk patients in trials lasting > 2 years. Still, these studies do not meet the criteria that pharmacological interventions must satisfy to be considered definitive. Further, most of these diets involved multiple, confounding recommendations and were assessed only

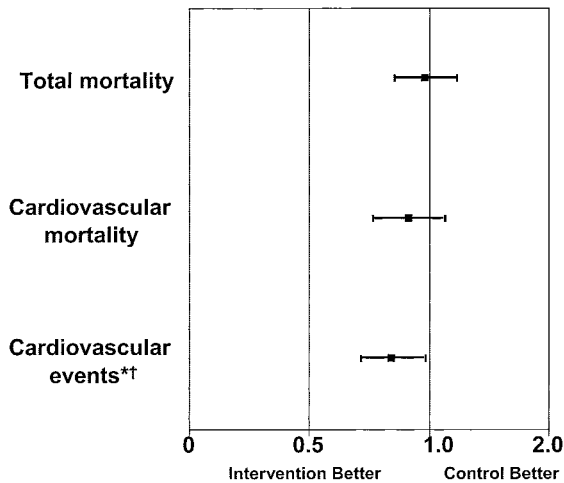


Figure 3. Rate ratios for outcomes of dietary intervention versus control, meta-analysis of 27 randomized studies.³⁰ *Cardiovascular death, nonfatal myocardial infarction, angina, stroke, heart failure, peripheral vascular events, or unplanned bypass surgery or angioplasty. †Nonsignificant after sensitivity analysis.

against normal or usual diets, not against one or more suggested dietary regimens.

One gains a sense of the inadequacy of available studies by reviewing some of the most commonly cited trials, several of which were included in the Cochrane review. In a very early study, 393 men recently discharged after a first MI were randomized to either their usual diet or one replacing saturated fats with polyunsaturated fats.²⁶ Patients on the test diet consumed an average 80 g (goal, 85 g) of soybean oil (a source of α -linolenic acid, an omega-3 fatty acid) daily and reduced saturated fats to 40 g (goal, 35 g) daily. Serum total cholesterol, but not triglycerides, decreased more in the test-diet group. During a follow-up that ranged from 2 to 7 years, the groups had similar rates of nonfatal and fatal cardiovascular events.

In a double-blind study, 846 veterans with and without CAD in a Los Angeles, Calif, domicile were randomized to either a conventional diet (40% of energy from fat) or a lower-fat, lower-cholesterol diet that mostly substituted unsaturated fats for saturated fats.²⁷ Diet changes were made in the cafeteria, but participants were not required to eat there and had access to other food sources. After 8 years, more men in the control group reached a cardiovascular end point; however, the groups did not differ significantly in overall mortality. Of note, after being discharged from the domicile, \approx 400 participants were lost to follow-up.

In another study, inpatients without known CAD at one psychiatric hospital in Finland received the normal hospital diet, whereas those at another psychiatric hospital received a diet lower in saturated fats and cholesterol and higher in polyunsaturated fats.²⁸ After 6 years, the institutions switched diets. After combining data from both hospitals, more patients reached the combined end point of coronary death or major electrocardiographic (ECG) changes during the normal-diet period, although the overall incidence was low (3.7% over 12 years). Oddly, serum cholesterol levels were lower while subjects ate the experimental diet, yet at the

hospital that began with this diet, baseline serum cholesterol levels were low (presumably on a normal diet) but increased dramatically after switching to the normal diet. Other drawbacks to this study include a constantly changing population and differences between groups in blood pressure, cigarette smoking, and use of psychiatric medications that can affect the ECG.

In the Oslo-Diet Heart Study, 412 men were randomized to either a cholesterol-lowering diet or a control diet 1 to 2 years after first MI.²⁹ Men randomized to the experimental diet—low in saturated fat (8.5% of daily energy intake) and cholesterol (264 mg/d) and high in polyunsaturated fats (20.7% of daily energy intake)—showed a 17.6% (3.7% in the control group) reduction in total cholesterol over 5 years of diet instruction. After 11 years, the experimental diet group had significantly fewer MI-related deaths, but overall mortality did not differ between groups.

The Diet And Reinfarction Trial (DART) randomized 2033 men to receive or not receive each of the following 3 recommendations after MI: (1) Reduce fat intake to 30% of total energy with an increased polyunsaturated fat–saturated fat ratio; (2) eat 2 portions of fatty fish weekly; or (3) increase fiber intake to 18 g daily.³⁰ After 2 years, advice on fat intake and fiber intake appeared not to affect mortality or cardiac events. Those randomized to receive advice to eat more fish did have improved survival.

The Indian Heart Study randomized 505 patients 24 to 48 hours after MI to usual care or a reduced-fat diet with increased intake of fruit, vegetables, nuts, and grains, and replacement of saturated fats with monounsaturated fats and α -linolenic acid.³¹ At 1 year, patients assigned to the plant-rich diet showed greater reductions from baseline in weight and cholesterol levels compared with patients eating typical diets. More importantly, those eating the plant-rich diet had significantly fewer cardiac events (25% versus 41%) and significantly lower overall mortality (10.2% versus 18.8%). These event rates are very high by usual standards, however, raising questions about the representativeness of this cohort.

The Lyon Diet Heart study randomized 605 French men and women with previous MI to either a Mediterranean diet or their usual diet, which was higher in saturated fat and cholesterol.³² The intervention diet was supplemented with canola (rapeseed) oil-based margarine, which is rich in α -linolenic acid. The intervention group also consumed more fiber, monounsaturated fats, fruits, and vegetables than the usual diet group and less dietary cholesterol and saturated fat. At 2 and 4 years, the intervention diet group had significantly reduced cardiovascular complications and mortality, although cardiac risk factors (serum lipids, blood pressure) were comparable between groups before and after enrollment.³³ Similar to the Lifestyle Heart Trial, however, participants knew their group assignments before consenting to participate, and the control group received no parallel intervention. The intervention group also was supplied with certain food products (margarine, oils) free of charge.

In primary prevention, the NIH-funded Multiple Risk Factor Intervention Trial (MRFIT) randomized 12 866 men at risk for CAD to receive an intervention that included advice about diet (saturated fat \leq 8% of total energy), treatment of

hypertension, and counseling for cigarette smoking, or usual care.³⁴ There was no evidence that recommending a lower-fat diet had any effect, although total and LDL cholesterol levels clearly related to the risk of adverse outcomes.

Other Dietary Interventions

In numerous epidemiological studies, increasing fiber intake has been associated with a lower risk of heart disease.^{35,36} These foods can lower LDL levels and improve insulin sensitivity.³⁷ In a randomized intervention study, however, reinfarction was not reduced at 2 years in patients with existing CAD assigned to a high-fiber diet.³⁰ More recently, the large Women's Health Study showed an inverse relation between dietary fiber intake and the risk of primary CAD events, even after adjustment for age and randomization assignment (vitamin E and aspirin).³⁸ This relation did not persist after adjustment for CAD risk factors, however. Long-term follow-up from the DART trial also failed to show an effect of fiber advice on total or CAD mortality after MI.³⁹

Antioxidants also have been proposed for secondary and primary prevention of CAD events. Several large, prospective cohort and randomized controlled studies, however, have shown no benefit from β -carotene, vitamin E, vitamin C, selenium, or multivitamin supplements in reducing the risk of CAD. These include such recognized trials as the Heart Outcomes Prevention Evaluation (HOPE)-1,⁴⁰ Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico-Prevenzione (GISSI-Prevenzione),⁴¹ the Heart Protection Study,⁴² and others.⁴³⁻⁴⁵

Perhaps the most promising nutritional intervention is omega-3 fatty acid supplementation. Both plant-based (α -linolenic acid) and fish-based (eicosapentaenoic acid and docosahexaenoic acid) supplements have shown benefit in secondary CAD prevention. In the GISSI-Prevenzione trial, subjects who took fish oil had a lower rate of the primary end point (death, nonfatal MI, or stroke) over 3.5 years compared with controls.⁴¹ In the Indian Experiment of Infarct Survival,⁴⁶ the fish oil group had fewer cardiac deaths at 1 year compared with controls (overall mortality was not reported). The most promising of the aforementioned low-fat diet interventions included omega-3 fatty acid supplementation as part of the intervention.³⁰⁻³² In the DART trial, however, although twice-weekly meals of fish greatly reduced overall mortality early after MI,³⁰ this strategy was associated with higher risk over the next 3 years.³⁹ With regard to primary prevention, the Nurse's Health Study, an observational study, recently reported significantly lower rates of both nonfatal MI and CAD death with higher levels of fish intake among 84 688 nurses over 16 years of follow-up.⁴⁷ A similar pattern was shown for intake of α -linolenic acid in the Nurse's Health Study⁴⁸ and in MRFIT.⁴⁹ Other potential interventions include the plant-derived phytonutrients (isoflavones, phytoestrogens, polyphenols), but prospective, controlled outcomes studies are lacking.^{50,51}

What about the relevance of trials of lipid-altering agents? Multiple trials of statins, fibrates, and cholestyramine have shown that drugs that reduce LDL cholesterol significantly improve survival and prevent atherosclerotic events. These drugs have many actions besides simple reduction of LDL

cholesterol, however, and some have questioned whether events are prevented more effectively by agents with a stronger effect on LDL cholesterol. Additionally, the recent Heart Protection Study reported that simvastatin reduced the incidence of secondary cardiac events even in patients with LDL levels that did not signify major risk.⁴² Thus, although the benefits of specific lipid-lowering drugs are unquestioned, the relation between these drug effects and the potential of diet to improve outcomes is unclear.

Suggested Approach

The time has come for dietary research to eschew the type of data that would no longer be accepted to recommend a drug for CAD prevention or treatment. In contrast to drugs, the basic building blocks of diet will not change in the foreseeable future; there are only a few food types within the basic food groups, and society has decided against broad experimentation beyond natural sources of foods. Thus, a definitive trial, even if it takes years to conduct, is highly unlikely to be made obsolete by a biological advance. Furthermore, several previous studies suggest that dietary interventions might reduce cardiovascular events as much as lipid-lowering drugs can.

A definitive trial should be done only after the diet meets some general criteria for efficacy. First, it should have a firm biological basis. Second, it should reduce one or more risk factors for CAD. Finally, it should be based on evidence that those who attempt the diet have better clinical outcomes than those who do not.

An advanced understanding of trial methods has overturned many of the erroneous principles that have made large outcomes trials in this arena prohibitively expensive. We now understand that the appropriate question for public policy is not "Can a particular diet affect clinical outcome if followed in a rigorous fashion?" but rather, "Does a program of dietary advice that can be followed by a typical person lead to fewer cardiovascular events?" The former, an explanatory type of trial, is of theoretical interest, but it is the latter, an effectiveness or pragmatic type of trial, that will answer the public-policy question.⁵²

The time has come to apply to diet research the same level of evidence required for other interventions. We believe that indications or claims made for weight loss or health improvement via diet—whether made by authors, the government, or associations—must be supported by 3 types of evidence: proof that the diet provides essential nutrients in actual patients, efficacy studies, and randomized, controlled trials with clinical events as end points.

We conclude with an example that illustrates some of the deficiencies and opportunities in the system. The National Heart, Lung, and Blood Institute (NHLBI)-supported Dietary Approaches to Stop Hypertension (DASH) trial randomized 459 people to one of 3 diets: a typical US diet; a diet rich in fruits and vegetables but otherwise similar to control; or a diet rich in fruits, vegetables, and low-fat dairy products, and low in saturated and total fat (the so-called DASH diet).⁵³ People on the DASH diet, hypertensive or not, showed the greatest reduction in blood pressure among the 3 groups. The DASH-sodium study then tested the DASH diet against the typical

US diet, with participants randomized to eat foods with high, intermediate, and low sodium levels for 30 consecutive days each, in random order.⁵⁴ People who ate the DASH diet at the lowest sodium level had the lowest blood pressure, lower than that in the DASH-diet group or the low-sodium group alone. More recently, retrospective analyses from DASH have shown that people on the DASH diet also had lower levels of homocysteine⁵⁵ and LDL and total cholesterol.⁵⁶

Clearly, the DASH diet can affect several body systems. Whether the changes in the putative surrogate biomarkers will translate into reduced mortality or strokes, however, especially among those with normal biomarkers at baseline, is unknown—the DASH studies were efficacy-feeding studies, not effectiveness studies. The diet also may not be feasible in the “real world.” To the credit of the NIH and the DASH investigators, the PREMIER study, the outpatient version of the DASH diet, has been funded and conducted. It completed enrollment only recently, however, and its results are not expected until 2003. More importantly, it does not have adequate statistical power to make a statement about clinical events. Nonetheless, the NHLBI now is urging people to “consider” the DASH diet for an overall eating plan.⁵⁷ Although the need to make recommendations is understandable, even without definitive knowledge, it would not be surprising if the DASH diet had no effect on CAD events despite its known metabolic effects. The only way to be sure is to assign participants randomly to the DASH diet versus another diet and measure outcomes in the 2 groups. Until then, the public will continue to be subject to speculation and potentially hazardous extrapolation from putative biological surrogates to clinical outcomes.

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