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Editorial

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“There is no human activity, eating, sleeping, drinking, or sex which some doctor somewhere won’t discover leads directly to cardiac arrest.”

John Mortimer

*British lawyer and writer
The Observer 1978*

This issue of *Dialogues in Cardiovascular Medicine* is devoted to *Lifestyle, Diet, and the Heart*, a subject that has received considerable impetus from the World Health Organization MONItoring trends and determinants in CARDIOvascular diseases (MONICA) project, a 10-year study of trends in disease and risk factors in 100 000 people in 21 countries. This, the largest ever study of cardiovascular disease confirmed smoking, high low-density lipoprotein (LDL) cholesterol, high blood pressure, lack of exercise, and obesity as major risk factors for the heart disease that kills millions of people annually. More recently, the INTERHEART study of 29 000 people in 52 countries added further support by identifying nine factors that collectively predict more than 90% of the risk of a heart attack. The factors: smoking, abnormal blood lipid ratios, high blood pressure, diabetes, obesity, stress, lack of fruit and vegetables and inadequate daily exercise point again to the importance of lifestyle as a determinant of cardiovascular disease. Several of these factors have already received our attention with issues of *Dialogues* devoted to *Atheroma* (and dietary lipid reduction) (1999), *Diabetes and the Heart* (2000), *Sport, Exercise, and the Heart* (2002), and the *Metabolic Syndrome* (2004). In this issue, we focus further on lifestyle and cardiovascular disease—the good, the bad, and the ugly. Dr Scott Grundy from the Center for Human Nutrition in Dallas has contributed enormously to our understanding of the biology of lipids and their role in the genesis of atherosclerotic cardiovascular disease. In his Lead Article, Dr Grundy provides compelling arguments for intensive public health preventative campaigns, hand-in-hand with clinical treatment, as a means of lowering cardiovascular risk in whole populations through the promotion of healthy lifestyles. Reflecting the conclusions of the MONICA project, he focuses on the benefits of smoking cessation, dietary lipid control, blood pressure lowering, weight reduction, and regular physical activity. He also ventures into the fascinating areas of herbal supplements and the possible benefits of moderate alcohol consumption. Dr Grundy’s article not only provides a comprehensive manual for ways





to optimize lifestyle and cardiovascular well-being, but also, in bemoaning the general neglect of proven lifestyle therapies, it clearly illustrates the vital role that can and must be played by health care professionals in reducing the epidemic of cardiovascular disease. Many questions, however, remain, and one of these relates to defining what is the optimal macronutrient consumption for combating coronary heart disease in general and the metabolic syndrome in particular. Professor Paul Nestel, a distinguished expert in nutritional science from the Baker institute in Melbourne, responds to this question by providing detailed consideration and recommendations relating to: reducing the intake of refined carbohydrates, emphasizing unsaturated and marine fatty acids, and the importance of substituting protein in the reduction of total fat. Next, Dr David Sheps from the University of Florida addresses the long held view that stress in various forms contributes to coronary disease. Dr Sheps has achieved international recognition for his pioneering work on psychosocial stress, caused for example by depression, as a risk factor for post–myocardial infarction mortality. He reveals how brief or extended events such as earthquakes, terrorist attacks, anger, and bereavement may contribute significantly to a range of cardiac events, including ventricular fibrillation. Our readers, reflecting on their own stresses of life caused perhaps by an overload of patients, a lack of patience, a rejected grant or manuscript might be forgiven for reaching for a glass or more of wine to sooth their psyche and raise their spirits. Well, read first the contribution by Dr Michael Criqui from the University of California, who, when not joining his fellow Californians worrying about earthquakes, has achieved recognition for his work on alcohol and the heart. While confirming that a small amount of alcohol may confer cardiovascular help to a small subset of the population, the dose-response curve is bell-shaped with the third drink sadly negating the benefit of its predecessors. He argues the risk-to-benefit ratio is such that alcohol would, without doubt, prevent its licensing by any drug regulatory authority. This, of course, poses many dilemmas to physicians in their quest to give appropriate advice to patients.

“There are two reasons for drinking; one is, when you are thirsty, to cure it; the other, when you are not thirsty, to prevent it... Prevention is better than cure!”

*Thomas Love Peacock
1789-1866
Melincourt Ch 6*

Prevention of atherosclerotic cardiovascular disease: why are the benefits of lifestyle therapies neglected?

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There are two approaches for reducing atherosclerotic cardiovascular disease (ASCVD): the population approach and the clinical strategy. The population approach attempts to lower risk in the whole population through promotion of healthy life habits. The clinical strategy is an extension of the population approach; it employs the same principles as the public health approach, but applied to patients at high enough risk for ASCVD to justify long-term risk reduction through clinical management. The population approach has provided consistent messages on cardiovascular risk reduction for over four decades. They emphasize avoidance or cessation of cigarette smoking, reduction of intakes of saturated fats and cholesterol, achieving and maintaining a healthy body weight, regular physical activity, and regular medical checkups for ASCVD risk factors. The use of regular medical checkups is vital for linking the population and clinical approaches. Unfortunately, the current health care system is lacking in clinical preventive strategies. However, if the overall strategy for ASCVD risk reduction is to be successful, this component will have to be strengthened greatly.

Keywords: cardiovascular disease; atherosclerosis; lifestyle management; prevention; risk factor; diet; metabolic syndrome; hypertension; obesity; smoking

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Physicians and other health professionals not only carry out clinical treatment, they are also vital members of a large public health team. For persons at low-to-moderate risk, every opportunity should be taken to impart the public health message on prevention. Health professions should reach beyond the individual patient to other members of the family. A physician's advice is always valued; it is certainly given more weight with individuals than mass media campaigns.

PRINCIPLES OF LIFESTYLE THERAPIES

The essential components of lifestyle therapies to reduce risk for atherosclerotic cardiovascular disease (ASCVD) are the following:

- Smoking cessation
- Dietary change to reduce low-density lipoprotein (LDL) cholesterol
 - Reduced intakes of saturated fats and cholesterol
 - Dietary adjuncts for enhancing LDL lowering (plant stanols/sterols and increased viscous [soluble] fiber)

SELECTED ABBREVIATIONS AND ACRONYMS

ALA	α -linolenic acid
ASCVD	atherosclerotic cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
NCEP	National Cholesterol Education Program
RDA	recommended daily allowance

- Dietary change to lower blood pressure (eg, DASH diet: Dietary Approaches to Stop Hypertension)
- Weight reduction
- Regular physical activity.

Smoking avoidance and cessation is the highest priority for lifestyle change. Beyond elimination of tobacco use, the dietary recommendation should reduce both LDL cholesterol and blood pressure. An increasing number of higher-risk patients present with the metabolic syndrome, and hence will require greater emphasis on weight reduction and increased physical activity. Lifestyle management of risk factors often is enhanced by referring patients to a qualified dietitian or exercise therapist. Smoking cessation programs also can be helpful for smokers.

Although there is no universal agreement on the preferred dietary pattern for reducing risk for ASCVD, a typical macronutrient composition of a therapeutic diet is as follows¹:

- Saturated fat → less than 7% of total calories
- Monounsaturated fat → up to 20% of total calories
- Polyunsaturated fat → up to 10% of total calories
- Total fat → 25% to 35% of total calories
- Carbohydrate → 50% to 60% of total calories
- Protein approximately → 15% of total calories.

In this diet, the fiber content should be 20 to 30 grams per day. Dietary cholesterol should be less than 200 mg/d. Dietary sodium should not exceed 2.4 g/d (100 mmol/d). Foods should be chosen that are rich in calcium and potassium. Alcohol intake should be limited to no more than 1 oz (30 mL) of ethanol, the equivalent of two drinks per day, in most men, and no more than 0.5 oz (30 mL) of ethanol (one drink) per day in women. Total calories should be limited to amounts required to maintain desirable body weight (body mass intake 18-25 kg/m²). The benefits of this "healthy" diet should be augmented by at least 30 min/d of moderate intensity physical activity.

These recommendations accord with most of those provided by nutritional guidelines. The rationale for the recommended composition of the therapeutic diet can be reviewed briefly. First the major components of an LDL-lowering diet will be discussed. This discussion will be amplified by suggestions for dietary treatment of hypertension. Then, other nutrient factors that may reduce risk for ASCVD will be considered. Finally, a few comments will be made about strategies to achieve weight reduction and increased physical activity in the clinical sphere.

THERAPEUTIC DIET DESIGNED TO REDUCE SERUM LDL CHOLESTEROL

An elevation of serum LDL is the primary lipid risk factor.¹ An abundance of evidence indicates that a high LDL level promotes the development of atherosclerosis at every stage including precipitation of major ASCVD events. Controlled clinical trials, moreover, have shown that reduction of LDL levels will substantially reduce the risk for ASCVD events. For these reasons, there is now almost universal agreement that strategies designed to lower LDL, or its surrogate LDL cholesterol, will reduce risk for future ASCVD events in higher risk persons.¹

According to current guidelines, the intensity of LDL-lowering therapy should be adjusted to the absolute risk of the patient. The United States National Cholesterol Education Program (NCEP) has recently extended this concept and updated its clinical guidelines for LDL-lowering therapy based on the finding of newer clinical trials.² The essential features of this update are shown in *Table I*. This table outlines categories of risk, treatment goals of LDL cholesterol, when to initiate dietary therapy, and when to consider drug therapy. In higher-risk patients, if the goals for LDL cholesterol cannot be achieved by dietary therapy alone (first-line therapy), it may be necessary to add cholesterol-lowering drugs to the treatment regimen. Indeed, in most patients at high risk, drug therapy will be required in addition to dietary management. Nonetheless, the benefits of dietary therapy go beyond LDL lowering; for this reason, they should not be neglected in patients who require drug treatment to achieve the LDL goals.

Adjustment of macronutrients for an LDL-lowering diet

The major LDL-raising dietary constituents are saturated fat and cholesterol. Their ability to raise the LDL cholesterol levels has been shown in many metabolic studies. Epidemiological studies³ further suggest that diets high in saturated fats and cholesterol contribute importantly to high risks of ASCVD in several nations—particularly in those of northern and western Europe and in the United States. A reduction in intakes of saturated fats and cholesterol will reduce the serum LDL cholesterol levels, and meta-analysis of dietary trials show that this reduction will reduce risk for major coronary events.⁴ The other major nutrients—unsaturated fats, protein, and carbohydrates—do not raise



Risk category	LDL-cholesterol goal	Initiate therapeutic lifestyle changes	Consider drug therapy ^g
High risk^a (10-year risk for CHD >20%) ^b	<100 mg/dL (optional goal: <70 mg/dL)	≥100 mg/dL ^f	≥100 mg/dL ^h (<100 mg/dL: consider drug options) ^h
Moderately high risk 2+ risk factors ^c (10-year risk for CHD 10% - 20%)	<130 mg/dL ^e	≥130 mg/dL ^f	≥130 mg/dL (100-129 mg/dL: consider drug options) ⁱ
Moderate risk 2+ risk factors ^c (10-year risk for CHD <10%)	<130 mg/dL	≥130 mg/dL	>160 mg/dL
0-1 risk factors ^d	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

^a High risk includes coronary heart disease (history of myocardial infarction, unstable angina, stable angina, coronary artery procedures (angioplasty or bypass surgery), or evidence of clinically significant myocardial ischemia) clinical manifestations of noncoronary forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and carotid artery disease [transient ischemic attacks or stroke of carotid origin or >50% obstruction of a carotid artery]), diabetes, and 2+ risk factors with 10-year risk for hard coronary heart disease (CHD) >20%.

^b 10-year risk for CHD is calculated by Framingham risk scoring.

^c Risk factors include cigarette smoking, hypertension (blood pressure ≥140/90 mm Hg or on antihypertensive medication), low high-density lipoprotein (HDL) cholesterol (<40 mg/dL), family history of premature CHD (CHD in male first-degree relative <55 years; CHD in female first-degree relative <65 years), and age (men ≥45 years; women ≥55 years).

^d Almost all people with 0-1 risk factor have a 10-year risk <10%, and 10-year risk assessment in people with 0-1 risk factor is thus not necessary.

^e Optional LDL cholesterol goal <100 mg/dL.

^f Any person at high-risk or moderately high risk who has lifestyle-related risk factors (eg, obesity, physical inactivity, elevated triglyceride, low HDL cholesterol, or metabolic syndrome) is a candidate for therapeutic lifestyle changes to modify these risk factors regardless of LDL cholesterol level.

^g When LDL-lowering drug therapy is employed, it is recommended that intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL cholesterol levels.

^h If baseline LDL cholesterol is <100 mg/dL, institution of an LDL-lowering drug is optional depending on clinical judgment. If a high-risk person has high triglycerides or low HDL cholesterol, combining a fibrate or nicotinic acid with an LDL-lowering drug can be considered.

Table 1. National Cholesterol Education Program (NCEP) low-density lipoprotein (LDL) cholesterol goals and cutpoints for therapeutic lifestyle changes and drug therapy in different risk categories, and proposed modifications based on recent clinical trial evidence.

the serum LDL cholesterol. Nevertheless, there are considerations for each of these other components in designing a therapeutic diet. These considerations can be described briefly.

Saturated fatty acids

Saturated fatty acids are the major macronutrient determinant of LDL cholesterol concentrations.⁵ Meta-analyses of dietary studies⁶ indicate that for every 1% increase in calories from saturated fatty acids, the serum LDL cholesterol rises about 2%. Likewise, a 1% reduction in saturated fatty acids reduces LDL cholesterol by about 2%. Reducing saturated fatty acids in the diet is not harmful. Large-scale randomized controlled trials⁷ have documented safety of reduced intakes of saturated fatty acids in children, without evidence of compromised growth or development. In addition, there

is an interaction between body weight and saturated-fat intake, ie, LDL cholesterol lowering from reducing saturated fat is enhanced by weight reduction in overweight persons.⁸

Not all saturated fatty acids have the same cholesterol-raising potential. The dominant cholesterol raising saturated acid is palmitic acid (C16:0). Another cholesterol raiser is myristic acid (C14:0).⁹ Shorter-chain saturated acids (C:10 and C:12) also raise the serum LDL cholesterol, but less so than palmitic and myristic acids.^{10,11} In contrast, stearic acid (C18:0) does not increase LDL cholesterol levels¹²; this is because it is rapidly converted to oleic acid (C18:1) once it enters the body.¹² In spite of these differences in cholesterol-raising properties, the saturated fatty acids are generally considered as a group rather than individually.

From population studies, it has been learned that consumption of high amounts of saturated fatty acids is associated with increased risk for coronary heart disease (CHD).³ Conversely, lowering serum cholesterol levels by decreasing intakes of saturated fatty acids in controlled trials reduces the risk for CHD. Gordon⁴ found in six robust dietary trials including 6356 persons that reducing dietary saturated fatty acids lowered the incidence of CHD by 24%, coronary mortality by 24%, and total mortality by 6%, without an increase in non-ASCVD mortality.

In Europe and the United States, the diet contains 11% to 15% of total calories as saturated fatty acids. These calories come from:

- High-fat dairy products
 - Whole milk
 - Cheese
 - Butter
 - Ice cream
 - Cream
- High-fat meats
 - Fatty meats such as regular ground beef (hamburger), processed meats (hot dogs, sausage, bacon)
 - High-fat luncheon meats (bologna, salami, chopped ham products)
 - Skin of poultry
- Tropical oils
 - Palm oil
 - Coconut oil
 - Palm kernel oil
- Baked products and mixed dishes containing dairy fats, shortening, and tropical oils.

In patients who are candidates for clinical LDL-lowering therapy it is feasible to lower intakes of saturated fatty acids to <7 percent of total energy.

Trans fatty acids

Trans fatty acids have double bonds in the *trans* configuration. When *trans* fatty acids are exchanged for unsaturated fatty acids, that raises the LDL cholesterol level similarly to saturated fatty acids.¹³ There are epidemiological studies suggesting that relatively high intakes of *trans* fatty acids are associated with increased risk for CHD; however, no clinical trials have been carried out that show that lowering of *trans* fatty acids will reduce risk for CHD. It is important to note that compared with saturated fat intake, the consumption of *trans* fatty acids is relatively low, eg, about 2.6% of total energy. For this reason, priority in reducing cholesterol-raising fatty acids should be placed on saturated fatty acids, not *trans* fatty acids. Still, some reduction

in *trans* intake could help to lower the average LDL cholesterol concentration in the population. To achieve this reduction, attention must be given to their sources. In the USA diet, for example, most of *trans* fatty acids in the diet are derived largely through consumption of products that contain hydrogenated vegetable oils:

- Margarines
- Shortenings
- Bakery goods using *trans*-rich shortenings.

Dietary cholesterol

Dietary cholesterol induces severe hypercholesterolemia in several animal species, including nonhuman primates. This phenomenon is not observed in humans, however. But contrary to what some people believe, metabolic studies in humans indicate that high cholesterol intakes can in fact raise LDL cholesterol concentrations.¹⁴ Although the human response is variable, on average, the rise of serum cholesterol to dietary cholesterol is approximately 10 mg/dL per 100 mg dietary cholesterol per 1000 kcal.¹⁴ In the United States population, dietary cholesterol intakes have declined progressively. These falls undoubtedly have contributed to a reduction in average serum cholesterol levels in the population. There has been a decreased intake of all the sources listed above. In the USA, the average daily consumption of cholesterol is 256 mg (331 mg for men and 213 mg for women). Any further reduction in serum cholesterol levels by reducing dietary cholesterol will require targeting of the main sources of cholesterol in the diet:

- Eggs
- Meats
- High-fat dairy products.

Monounsaturated fatty acids

Monounsaturated fatty acids in the diet consist largely of oleic acid (a *cis* fatty acid). In the typical diet, monounsaturated fatty acids come from both animal and plant oils. The major plant oils that contain monounsaturated fatty acids are:

- Olive oil
- Rapeseed oil
- High-oleic safflower oil
- Peanut oil.

Substitution of dietary oleic acid for saturated fatty acids results in a fall in LDL cholesterol.^{15,16} This exchange causes little or no decrease in high-density lipoprotein (HDL) cholesterol or rise in serum triglyceride. This lack of change in HDL and triglyceride contrasts with the fall in HDL cholesterol and the rise in triglyceride when carbohydrates are substituted for



saturated fatty acids. The possibility of increased consumption of monounsaturated acids in the form of vegetable oil is attractive as one healthy dietary alternative, the so-called Mediterranean diet. For example, it has been noted that rates of CHD are low in the Mediterranean basin where large amounts of monounsaturated-rich olive oil are consumed.

Polyunsaturated fatty acids

Polyunsaturated fatty acids in the typical diet consist mainly of n-6 linoleic acid (C18:2). This fatty acid comes exclusively from plant products. Examples of plant oils that are rich in polyunsaturated fatty acids are:

- Corn oil
- Soybean oil
- High-oleic safflower oil.

Like oleic acid, dietary linoleic acid reduces LDL cholesterol when exchanged for saturated fatty acids.^{6,15} There has been considerable dispute whether linoleic acid reduces LDL cholesterol more than oleic acid when substituted for saturated fatty acid. If so, the differences are small.^{6,15} One potential reason to favor linoleic acid over oleic acid in the diet is that meta-analysis of several controlled trials has shown that substituting linoleic acid for saturated fatty acids reduces risk for CHD.⁴ Such trials have never been carried out with oleic acid substitution.

Despite this clinical trial evidence, no large populations have consumed large quantities of polyunsaturated fatty acids for long periods. This contrasts with the high intakes of oleic acid in the Mediterranean region. For this reason, recommendations for raise intakes of linoleic acid much above current levels of intake have not been forthcoming.

Total fat

In spite of a widely held view that high intakes of total fat will raise the LDL cholesterol level, the data restrict cholesterol-raising fats to saturated and *trans* fats.¹⁷ Thus, other reasons have been suggested for limiting fat intake to a moderate range. For example, it has been postulated that high intakes of total fat will promote weight gain, favor increased intake of saturated fatty acids, and perhaps predispose to cancer. On the other hand, there may be a downside to low-fat/high-carbohydrate diets. For example, some investigators believe that recommendations to reduce fat intake have contributed to overconsumption of carbohydrates; if so, excess carbohydrate calories could have actually contributed to weight gain observed in recent years in the United States population. There also may be metabolic

abnormalities (to be discussed below) caused by high carbohydrate diets. For these reasons, further research will be required to determine what is the desirable ratio of total fat-to-carbohydrate in the diet.¹⁷

Carbohydrate

Substitution of carbohydrates causes a reduction of LDL cholesterol levels comparable to that seen with monounsaturated fatty acids.^{16,17} In contrast, however, substituting carbohydrate for saturated fatty acids often reduces HDL cholesterol and raises triglyceride. This effect, moreover, is persistent. Changes in HDL cholesterol and triglyceride may be partially mitigated when high-carbohydrate diets are enriched with viscous fiber. Moreover, whole grains, vegetables, and some fruits contain viscous fiber, which has LDL-lowering properties. Some investigators suggest that different forms of carbohydrate differ in "glycemic" potential, that is, by their ability to raise plasma glucose. Still, the concept of "glycemic index" as a way to select specific carbohydrate-containing foods for dietary therapy is not widely accepted.

Dietary protein

Dietary protein in general does not affect LDL cholesterol levels; an exception may be soy protein which has small LDL-lowering effect.¹⁸ In any case, it is important to choose sources of protein for the diet that do not carry other factors (eg, saturated fats) that raise the LDL cholesterol levels. Examples of high protein sources to use in LDL-lowering dietary therapy are legumes, dry beans, nuts, grain products and vegetables, fat-free and low-fat dairy products, egg whites, fish, skinless poultry, and lean meats.

Dietary adjuncts to an LDL-lowering diet

Increasing viscous fiber in the diet. Adding 5 to 10 grams of viscous fiber to the diet will reduce LDL cholesterol by approximately 5%.¹ Insoluble fiber has no effect on LDL cholesterol. Good sources of fiber of the viscous type include:

- Cereal grains (barley, oatmeal, oat bran, seeds)
- Fruit (especially apples, banana, peaches, pears, plums, prunes)
- Legumes (beans, lentils, peas)
- Vegetables (broccoli, brussels sprouts, carrots).

Plant sterols/stanols

Sterols derived from plants (phytosterols) have been known to lower serum cholesterol for many years. The mechanism is through interfering with absorption of

intestinal cholesterol. In recent years, several advances have been made in implementation of their use in LDL-lowering diets. For example, phytosterols can be esterified to unsaturated fatty acids (creating sterol esters) to enhance lipid solubility (eg, dissolving them in margarines). Better LDL lowering is possibly obtained by hydrogenating sterols produces plant stanols; these in turn can be esterified to produce stanol esters. At present, there are no definitive data to show a difference in LDL-lowering potential between plant sterols and plant stanols.¹⁹ Recent research shows that administration of 2 g/day of stanols/sterols in ester form will lower LDL cholesterol on average about 10%, or in some persons, up to 15%.¹⁹ To date, no significant side effects have been attributed to daily consumption of stanols/sterols at the 2 g/day level.

LDL lowering through weight reduction

Weight reduction may or may not reduce LDL cholesterol levels in an individual. There is variable susceptibility in response of LDL cholesterol levels to weight loss. Nonetheless, when a reduction in intakes of saturated fatty acids is accompanied by weight reduction, LDL lowering is enhanced.⁸ It should also be noted that weight reduction will reduce total serum levels of apolipoprotein B (apoB). This means that the number of atherogenic lipoprotein particles is reduced by weight loss. The benefit from this reduction in fact is greater than reflected in the lowering of LDL cholesterol. Thus, weight reduction should be an integral part of a diet designed to lower LDL cholesterol and atherogenic lipoproteins.

Maximal dietary therapy for LDL lowering

In view of growing evidence of “the lower, the better” for LDL cholesterol, the potential power of dietary therapy to reduce serum LDL cholesterol levels cannot be ignored by the physician. Intensive dietary therapy (maximal dietary therapy) can produce substantial reductions in LDL cholesterol, whether used alone or in combination with LDL-lowering drugs. In addition, maximal dietary therapy can reduce risk for ASCVD in ways other than through LDL lowering. The theoretical benefit of dietary therapy is revealed by populations that consume low intakes of saturated fats and cholesterol and who maintain desirable body weight.³ In these populations, rates of ASCVD are relatively low compared with those populations that habitually consume LDL-raising diets.⁴ Recently, Jenkins and coworkers²⁰

have demonstrated that dietary adjustment can in fact reduce LDL cholesterol levels in the range of that produced by moderate doses of statins. An example of the additive effects of combination of LDL-lowering approaches is shown by the following estimates:

Dietary change	LDL cholesterol decrease
• Saturated fat (<7% of calories)	8%-10%
• Dietary cholesterol (<200 mg/day)	3%-5%
• Weight loss (10 pounds)	5%-8%
• Viscous fiber (5-10 g/day)	5%-8%
• Plant stanol/sterol esters (2 g/day)	7%-15%
• Total LDL cholesterol decrease	20%-30%

From clinical trial data, it has been shown that for every 1% lowering of LDL cholesterol, the risk for major CHD events is reduced by 1%.¹ Thus, the magnitude of risk reduction that can be achieved by the above dietary changes is considerable.

DIETARY THERAPY FOR PATIENTS WITH HYPERTENSION (DASH DIET)

Elevations in blood pressure and serum cholesterol often go together. Moreover, persons with blood pressures in the range of 120-139/80-89 mm Hg (prehypertension) can reduce their chances of developing frank hypertension by consuming less salt and by consuming foods relatively high in potassium, calcium, and magnesium.²¹ Likewise, daily adherence to such a diet can significantly reduce blood pressure in hypertensive patients.²¹ The effectiveness of such a diet has been shown in the Dietary Approaches to Stop Hypertension (DASH) trial.²² The major components of the DASH diet are:

- Reduced sodium intake to 1800 to 2400 mg/day
- Consumption of foods rich in potassium, calcium, and magnesium
 - Fruits and vegetables
 - Dairy products low in fat
 - Whole grains
 - Fish, poultry, and nuts.

If these components are increased in the diet, it is necessary to reduce other caloric sources that are less healthy, namely, those products listed previously that are rich in saturated fatty acids and cholesterol.

Many studies have shown that blood pressure can be significantly reduced through lifestyle changes. The following includes an approximation of the benefits in blood pressure lowering that can be achieved by lifestyle modification²¹:



Lifestyle modification	Systolic blood pressure reduction
• Achieve desirable weight	5-20 mm Hg per 10 kg weight loss
• Adopt DASH eating plan	8-14 mm Hg
• Limit dietary sodium (<100 mmol/d)	2-8 mm Hg
• Regular exercise (30 min/d)	4-9 mm Hg
• Limit ethanol consumption	2-4 mm Hg

The benefit in terms of cardiovascular disease of blood pressure lowering in the ranges shown above can be considerable. For example, it has been estimated that achieving a sustained 12 mm Hg reduction in systolic blood pressure over 10 years will prevent 1 death for every 11 patients treated.²¹

OTHER DIETARY FACTORS THAT MAY REDUCE RISK FOR ASCVD

There has been a great interest in the possibility that other dietary factors beyond those already discussed can reduce baseline risk for ASCVD. The possibility of influence of other factors is raised by studies on the dietary patterns in different populations. For instance, in the Mediterranean region, the diet has been traditionally enriched with fruits and vegetables, whole grains, ocean fish, and monounsaturated fatty acids; and where the traditional diet has been consumed, the risk for ASCVD appears to be lower than predicted by the major risk factors. Conversely, in Eastern Europe and Russia, rates of ASCVD are seemingly higher than would be predicted by risk factors. These findings are suggestive of the influence of other factors on ASCVD risk. Some support for this concept comes from studies of other types: laboratory, human studies, and clinical trials. The evidence related to specific categories of nutrients can be examined briefly.

n-3 (omega-3) polyunsaturated fatty acids

Polyunsaturated fatty acids of the n-3 (omega-3) type consist of α -linolenic acid (18:3) (ALA), eicosapentaenoic acid (EPA) (20:5), and docosahexaenoic acid (DHA) (22:6). Common sources of ALA are:

- High-source vegetable oils (evening primrose oil and flax seed oil)
- Moderate-source vegetable oils (soybean and canola oil).

In the body, some of the ALA is converted into EPA and DHA. The latter appear to be mainly the biologically active forms of n-3 fatty acids. EPA and DHA can be

obtained more directly from certain fish or from capsules enriched in these fatty acids. The types of fish that are enriched in EPA and DHA are:

- High concentrations: herring, sardine, anchovy
- Medium concentrations: salmon
- Lower concentrations: sole, halibut, cod.

It has been noted that some fish carry a content of mercury; thus, consideration must be given to the possibility that any protective effects of fish will be offset by the dangers of mercury toxicity. To avoid this danger, EPA and DHA can be obtained in capsule form. The relative amounts and proportions of EPA and DHA vary in different commercial preparations. At the present time, it is uncertain which preparation is preferable, and no blanket recommendation can be made.

Several epidemiological studies suggest an association between moderate fish consumption and reduced sudden cardiac death or ASCVD death.²³ This relationship, however, has not been observed universally. Postulated protective mechanisms for n-3 fatty acids are prevention of cardiac arrhythmias, reduced platelet aggregation, favorable inflammatory responses, and reduction in serum triglyceride levels. Support for the positive population studies comes from results of four clinical trials in which n-3 fatty acids were increased. The secondary prevention Diet And Reinfarction Trial (DART)²⁴ advised subjects to regularly consume fatty fish. The subjects in the fish group showed a 29% reduction in total mortality after 2 years, compared with a group that did not have increased fish intake. Second, the Lyon Heart Trial²⁵ tested a "Mediterranean" diet enriched with ALA in patients with established CHD. Compared with the control group, consumption of the Mediterranean diet resulted in fewer coronary events. The authors suggested that the favorable results might be explained by a higher intake of ALA. Third, Singh et al²⁶ treated patients with acute myocardial infarction with fish oil capsules (EPA 1.08 g/day) or mustard oil (α -linolenic acid 2.9 g/day) or placebo. Total cardiac events were significantly less in the groups on fish oil and mustard seed oil supplements. And fourth, the Italian Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico GISSI Prevention trial²⁷ tested fish oil supplements containing EPA and DHA (1 g/day fish oil) in 2836 subjects with established CHD; coronary outcomes were compared with those of 2828 control subjects. Fish-oil supplementation resulted in a 14% reduction in total death and a 17% reduction in cardiovascular death. Follow-up studies of GISSI suggested that most of the benefit was due to early prevention of sudden cardiac death. This finding is consistent

with the idea that n-3 fatty acids have an antiarrhythmic effect. On the basis of these trials, the American Heart Association favors use of fish oil supplements in patients with established CHD. But the strength of the evidence supporting use of fish oil in secondary prevention certainly is not as strong as that for standard modalities of treatment such as cholesterol-lowering drugs, antihypertensive agents, and aspirin.

Folic acid and vitamins B₆ and B₁₂

Folic acid and vitamins B₆ and B₁₂ (see reference 1) could play a protective role through their ability to reduce homocysteine levels. This is because several studies have suggested that high levels of homocysteine may raise the risk for ASCVD events. At the present time, however, it has not been determined through controlled clinical trials that supplementation of the diet with folate, B₆, and B₁₂ reduce risk for ASCVD. It is interesting to note that the Framingham Heart Study reports the mandated fortification of cereal grains with folic acid has reduced both the population mean homocysteine levels and the prevalence of hyperhomocysteinemia. Finally the recommended dietary allowance (RDA) for folate is 400 micrograms per day. It is advisable to make certain that all persons at risk for ASCVD are consuming this level of folate daily. On the other hand, intakes probably should not exceed 1000 micrograms per day to avoid masking vitamin B₁₂ deficiency.

Antioxidants

Experimental studies suggest that oxidation of LDL is an important step in the development and progression of CHD. Moreover, it appears that oxidation of LDL can be retarded by use of antioxidants (eg, ascorbic acid [vitamin C], α -tocopherol [vitamin E], β -carotene, ubiquinone [coenzyme Q10], bioflavonoids, and selenium). Experiments in laboratory animals find evidence of protective effects of antioxidants against development of atherosclerosis. Several epidemiological studies add support to this concept. In the past few years, a series of clinical trials, including one large trial²⁸ have been carried out to determine whether various antioxidant regimens will prevent ASCVD or other disease outcomes. To date, the findings are not encouraging. Although some of the trials gave suggestive evidence of benefit, most were negative, or in the case of β -carotene, suggestive of harm. For this reason, enthusiasm for use of antioxidants in the form of dietary supplements to prevent ASCVD has been dampened. These trials however may not be the final word on the issue. Prevention of oxidant stress is still a potential pathway

to prevention of ASCVD. But more efficacious antioxidants are needed along with more robust clinical trials to test their efficacy. At present, nonetheless, a strong recommendation cannot be made for use of antioxidants to reduce risk for ASCVD events in the short term. It is clear that currently available antioxidants do not have the power to reduce ASCVD similarly to what can be obtained with LDL-lowering drugs, antihypertensive agents, and aspirin. Thus, at most, use of antioxidants for the purpose of reducing risk for ASCVD must fall into the category of a therapeutic option, but is not a strong recommendation.

Alcohol

A large body of epidemiological data indicate that moderate alcohol consumption is associated with lower risk for CHD death.²⁹ The relation of alcohol to total mortality is J-shaped, suggesting that high intakes are harmful. In other words, moderate alcohol consumption associates with lower CHD mortality, and higher consumption with total higher mortality. Seemingly, the "protective" effect of alcohol is not related to the type of alcoholic beverages consumed. An important question is what constitutes a moderate alcohol intake. Current guidelines defines "moderate" as no more than one drink per day for women and no more than two drinks per day for men. The mechanisms underlying the putative protective of alcohol are not known, but several mechanisms have been proposed (eg, increases in HDL cholesterol, improvement in hemostatic factors, reduction in insulin resistance).

There are two reasons to mitigate specific recommendations to encourage alcohol intake to reduce risk for ASCVD: (i) all of the evidence comes from epidemiological evidence, which may be confounded by other factors; and (ii) the dangers of overconsumption of alcohol. Among the latter are increases in blood pressure, arrhythmias, myocardial dysfunction, acute pancreatitis, cirrhosis of the liver, and some forms of cancer, not to mention many others.

Herbal or botanical dietary supplements

In Western society, and likely in other societies, use of dietary supplements abounds. It is widely believed that these supplements promote health and reduce the risk of disease, including ASCVD. Commonly used herbal or botanical dietary supplements are cranberry, *Echinacea*, evening primrose, garlic, ginkgo, ginseng, goldenseal, grape seed extract, St John's wort, and saw palmetto. In spite of widespread use, there is little sci-



entific evidence of either efficacy or safety. Even the quality (purity) of many of products sold in health food stores, pharmacies, and many supermarkets is open to question. There have been a few attempts to test their efficacy for affecting various biomarkers, such as serum cholesterol, but the findings of these studies is far from convincing.

MANAGEMENT OF THE METABOLIC SYNDROME THROUGH LIFESTYLE THERAPIES

The NCEP identified the metabolic syndrome as a risk-factor partner of elevated LDL cholesterol.¹ The metabolic syndrome is a constellation of risk factors for ASCVD occurring in one person. There are five metabolic risk factors that constitute this syndrome:

- Atherogenic dyslipidemia
- Elevated blood pressure
- Elevated plasma glucose
- Prothrombotic state
- Proinflammatory state.

Atherogenic dyslipidemia is composed of four lipoprotein abnormalities: (i) elevated triglyceride; (ii) elevated apolipoprotein B (apoB); (iii) elevated small LDL particles; and (iv) reduced HDL. Patients with the metabolic syndrome often have only moderate elevations of blood pressure. The plasma glucose can be only moderately elevated in the fasting state (impaired fasting glucose [IFG]) or in the post-glucose challenge (impaired glucose tolerance [IGT]) or markedly elevated (type 2 diabetes). A prothrombotic state represents elevations of several factors affecting coagulation—plasminogen activator inhibitor-1 (PAI-1), fibrinogen, factor VII, and others. A proinflammatory state is secondary to increased tissue and circulating cytokines. This state is typically recognized by the presence of elevations of C-reactive protein (CRP).³⁰ The presence of these metabolic abnormalities confers increased risk for ASCVD; they also are associated with increased risk for type 2 diabetes. The elevation of plasma glucose of type 2 diabetes is in addition a risk factor for ASCVD. Patients with the metabolic syndrome often have a fatty liver as well.

The metabolic syndrome has a multifactorial etiology, of which obesity is a major factor. Most persons with the metabolic syndrome have two underlying causes: obesity (especially abdominal obesity) and insulin resistance.³¹ Obesity itself can cause insulin resistance, but people who have an inherent insulin resistance

can develop the metabolic syndrome with only mild obesity. Details of the pathogenesis of the metabolic syndrome are not fully worked out. However, it is quite clear that weight reduction will mitigate the metabolic risk factors in most patients. Other factors—lack of exercise, aging, and hormonal imbalance appear to contribute to the development of the metabolic syndrome. Further, in persons who have genetic abnormalities affecting individual risk factors, the severity of the risk factor can be enhanced by the presence of obesity/insulin resistance.

The distribution of body fat is somehow related to the metabolic syndrome. For example, most people with the metabolic syndrome exhibit abdominal obesity. Investigators differ as to whether intraperitoneal (visceral) obesity or abdominal subcutaneous obesity is the most important. It is likely that excess fat in both adipose tissue beds of the abdomen contributes to the syndrome.

The NCEP¹ proposed to identify patients with the metabolic syndrome clinically by the presence of several simple clinical measures. Thus, a patient is said to have the metabolic syndrome if he/she has any three of the following five characteristics:

- Abdominal obesity (waist circumference ≥ 102 cm in men; ≥ 88 cm in women)
- Elevated triglyceride (≥ 150 mg/dL)
- Reduced HDL-C (< 40 mg/dL in men; < 50 mg/dL in women)
- Elevated blood pressure (≥ 130 mm Hg systolic or ≥ 85 mm Hg diastolic)
- Elevated fasting plasma glucose (≥ 100 mg/dL).

Any person who has the metabolic syndrome by these characteristics can be considered to be at high lifetime risk for both ASCVD and type 2 diabetes. For this reason, such a person should be entered into clinical management of underlying risk factors on a long-term basis. This includes both managed weight reduction and increased physical activity. This section will address the lifestyle approach to treatment of the metabolic syndrome. Some patients with the metabolic syndrome will be at high enough risk to initiate drug therapy to control risk factors. For example, most persons with categorical hypertension (blood pressure $\geq 140/90$ mm Hg) will require antihypertensive drugs if their blood pressure cannot be reduced below these cutpoints by lifestyle change.²¹ For elevated LDL cholesterol, the guidelines outlined in *Table I* should be followed.^{1,2} LDL-lowering drugs usually will be required for patients at high risk, ie, those with ASCVD and diabetes. For

subjects below the high-risk category, risk assessment by Framingham risk scoring or comparable algorithms should be determined to define absolute risk. Then lipid-lowering drug therapy should be employed according to the guidelines suggested in *Table I*. Finally, for individuals who have a 10-year risk for CHD $\geq 10\%$, institution of aspirin therapy is a therapeutic option.³²

WEIGHT CONTROL IN PERSONS WITH THE METABOLIC SYNDROME

Current recommendations³³ for treatment of obesity emphasize three modalities:

- Reduced caloric intake
- Increased physical activity
- Behavioral modification.

In cases of severe obesity, weight-reduction drugs and bariatric surgery—may be necessary.

Weight-loss diets

Several key points can be made about weight-reduction diets^{1,33} for patients with the metabolic syndrome:

- The primary goal
 - Achieve approximately 7% to 10% reduction in body weight in first year of treatment
 - Thereafter, continue slow weight loss to attain a body mass index (BMI) of $< 25 \text{ kg/m}^2$
- Reduce current caloric intake by 500 to 1000 calories per day
 - Avoid extremes of caloric restriction (eg, “crash diets,” “very-low-calorie diets)
- Consume a diet with balanced macronutrients
 - Consider employing a fat intake of about 35% of calories
 - Keep saturated fatty acids low; use mainly unsaturated fatty acids as fat source
 - Avoid extremes of diet composition
- Initiate long-term follow-up and monitoring.

Periodically, weight-loss diets high in protein and fat and low in carbohydrate surge are commercially promoted. These diets often required extremes of caloric restriction. They can achieve considerable weight loss during the first few weeks or months. In spite of this early “success,” they have not been shown to yield long-term weight loss. If these “diets” are employed for relatively short periods, they likely will not produce lasting side effects. On the other hand, they may lead to repeated efforts at rapid weight loss (yo-yo dieting), or they may engender a sense of failure after initial euphoria. Therefore, regardless of diet composition, more

extreme diets should be avoided. In addition, several other concerns can be raised about their use for weight reduction. For example, high intakes of saturated fats in some high-fat weight loss diets can raise LDL cholesterol. And low intakes of fruits, vegetables, and grains can deprive one of healthful nutrients.

These so-called low-carbohydrate, high-fat, high-protein regimens for rapid weight loss must be distinguished from the recommendation to employ a fat intake of about 35% of total calories. Importantly saturated fatty acids should be kept low ($< 7\%$ of total energy) and most of the fat should be unsaturated. This level of fat intake will prevent the effects of a high-carbohydrate diet to raise triglycerides and reduce HDL cholesterol levels. Beyond fat content the diet should be reduced in simple sugars and enriched in fruits, vegetables, and whole grains.

Increased physical activity

Without a regimen of regular exercise, long-term weight loss is difficult to maintain. Besides promoting and maintaining weight loss, regular physical activity will help to reduce the risk factors of the metabolic syndrome. More detail on how to carry out increased physical activity will be given in the section to follow.

Behavioral modification

To achieve long-term weight loss, a person’s behavior must be modified.³³ The concept that weight can be lost rapidly and the lower body weight will be maintained automatically has been shown many times to be fallacious. Dietitians seem to be the type of health professional most likely to achieve behavior modification. However, more attention needs to be given to this problem in research, and new approaches need to be developed. A few general techniques, nonetheless, have been identified and can be employed at present:

- Setting realistic goals for change
- Systematic planning of meals
- Careful reading of food labels
- Eating at regular times
- Reducing portion sizes
- Self-monitoring of eating patterns
- Learning to avoid eating binges.

Guidelines for weight reduction with valuable information have been developed by government panels and other organizations. This information can be downloaded from several websites including www.nhlbi.nih.gov and www.americanheart.org.



INCREASED REGULAR PHYSICAL ACTIVITY

Physical inactivity is a major underlying risk factor for ASCVD.³⁴ The benefits of increasing physical activity on ASCVD risk are likely mediated through several factors—both cardiovascular and metabolic. Physical inactivity certainly impairs cardiovascular fitness, and it may adversely affect coronary blood flow. In patients with the metabolic syndrome, increased physical activity will reduce the severity of all of the ASCVD risk factors. For this reason, in patients who are identified as having the metabolic syndrome, physicians should take advantage of benefits of physical activity in treatment. For example, a physician can refer the patient to an exercise specialist for prescription and guidance in exercise training. Some of the advice to give to patients with the metabolic syndrome is to encourage them to add various forms of physical activity to their daily lives. Examples of types of exercise that should be beneficial are:

- Brisk walking (3–4 mph) for 30 to 40 minutes
- Swimming: laps for 20 minutes
- Bicycling for pleasure or transportation, 5 miles in 30 minutes
- Volleyball (noncompetitive) for 45 minutes
- Raking leaves for 30 minutes
- Moderate lawn mowing (push a powered mower) for 30 minutes
- Home care: heavy cleaning
- Basketball for 15 to 20 minutes
- Golf: pulling a cart or carrying clubs
- Social dancing for 30 minutes.

PRACTICAL APPROACHES TO LIFESTYLE THERAPIES AND THE ROLE OF HEALTH PROFESSIONALS

Physicians

Lifestyle therapies cannot be successful without a commitment of the physician. Although the physician often will not have the time to counsel patients on the details of lifestyle change, he/she must set the process into motion. A positive attitude is essential to convince the patient that lifestyle changes are a necessary part of any preventive regimen. The many benefits of lifestyle modification must be stressed. But starting the process is not enough. Long-term follow-up and monitoring of the patient's life habit changes are necessary. This effort will require some time on the part of the physician, who should be willing to take on this added responsibility. The following is a list of topics that the

physician should consider when discussing lifestyle change with patients:

- Attention should be given to controlling ALL risk factors
- In primary prevention, dietary therapy should be tried for about 4 months before starting on drug treatment
 - If drugs are used, the need for dietary therapy is not diminished
 - Dietary therapy can enhance the effects of drugs
- Consideration should be given to referring the patient to a dietitian or other health professional trained in lifestyle change
- A multifactorial approach to lifestyle change (anti-atherogenic diet, weight reduction, increased physical activity) must be emphasized
- An understanding of the causes of poor response to lifestyle change is needed. Common causes include
 - Poor adherence to the therapy
 - Abrupt change often fails; gradual change is more effective
 - Some persons are inherently unresponsive to lifestyle change
 - Time for adjustment to dietary therapy is too short—and should be extended.

Nurses, physician assistants, and pharmacists

A physician's reach can be extended by involvement of other health professionals—nurses, physician assistants, nurse clinicians, pharmacists, and others. These individuals can provide education and monitoring to patients. They can be available to assist patients in ways not possible by physicians. For this reason, it will be necessary to provide education to these professionals so that they will be able to function effectively in working with patients.

Qualified nutrition professionals (dietitians)

In this review, qualified nutrition professionals will be called dietitians. The role of the dietitian is to carry out a comprehensive assessment of a patient's nutritional history and status and to prescribe a personalized course of treatment.

Nutritional assessment must take into account dietary history, cultural influences, current eating habits, weight history, and current weight.¹ Among questions to be asked in nutritional assessment are: (i) What times of the day does the patient usually eat? (ii) Are some meals routinely skipped? (iii) At what time does the

patient eat his/her largest meal? (iv) Where are meals typically prepared and eaten (eg, in a restaurant, work cafeteria, fast-food restaurant, deli, at home, or in the homes of others)? (v) Are there occasions when stress increases food consumption? (vi) Are meals eaten at home purchased out and brought in, prepared from processed prepackaged foods, or prepared fresh from the market? (vii) Which are favorite foods and what foods are disliked? (viii) Who is responsible for food shopping and preparation? (ix) What foods will be most difficult to increase or decrease? and (x) How well does the patient recognize serving sizes? Answers to these questions are needed to prepare the dietitian for working with the patient in lifestyle modification.

Following nutritional assessment, several issues must be discussed with the patient to initiate dietary therapy:

- Identification of foods in the diet that raise LDL cholesterol levels
 - Identification of “hidden fats” in the diet that raise cholesterol levels
- Discussion of alternatives for these foods
 - Fruits, vegetables, low-fat protein sources, unsaturated fats
- Definitions and significance of various food groups
 - Breads, cereals, pasta, whole grains, potatoes, rice, dry peas, beans
 - Fruits and vegetables
 - Low-fat dairy products
 - Lean meats and high-protein meat substitutes
 - Fats, oils, and nuts
- Monitoring and tracking of dietary change
- Approaches to weight reduction
- Education on measurements of portion sizes and reading of labels
- Discussion of problems associated with “eating out” of the home

- Developing a supportive social system (eg, parents, spouse, children)
- Attention to cultural differences and adjustment of therapeutic diet accordingly
- Education in food preparation techniques
- Necessity of gradual change.

ATTENTION TO ADHERENCE

All of the health professions involved in ASCVD prevention must give greater attention to the problem of adherence. There are many barriers to adherence in our society. Examples are eating away from home, obtaining foods prepared outside the home, lack of professional belief in effectiveness of lifestyle therapy, inadequate nutritional education on the part of both patients and professionals, unavailable referral resources, lack of reimbursement for lifestyle therapies, pressures to resort on drugs, inadequate time for professional follow-up. Studies have been carried out on strategies to improve adherence. Some of the findings of these studies should be taken into consideration. For example, strategies that have multiple components are more effective than those with a single approach. Increasing professional contact with patients improves adherence. Moreover, the more intense the intervention, the more effective it will be. Goal setting is an important component of a successful strategy. Self-monitoring efforts appear to improve adherence. These are just some of the ways to improve long-term outcome of lifestyle therapies. But most importantly, both the medical profession and the community at large must recognize that a major social commitment to improving health is need, followed by actions to acquire the resources needed to improve cardiovascular health. Without a society commitment, it will be difficult for physicians and other health professionals to be fully effective in preventive strategies.



REFERENCES

- 1. NCEP Expert Panel.**
Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report.
Circulation. 2002;106:314363421.

- 2. Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association.**
Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines.
Circulation. 2004;110:227-239.

- 3. Keys A, Menotti A, Aravanis C, et al.**
The Seven Countries Study: 2,289 deaths in 15 years.
Prev Med. 1984;13:141-154.

- 4. Gordon DJ.**
Cholesterol lowering reduces mortality: the statins. In: Grundy SM, ed. *Cholesterol-Lowering Therapy: Evaluation of Clinical Trial Evidence.* New York, NY: Marcel Dekker Inc; 2000:299-311.

- 5. Grundy SM, Denke MA.**
Dietary influences on serum lipids and lipoproteins.
J Lipid Res. 1990;31:1149-1172.

- 6. Mensink RP, Katan MB.**
Effects of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials.
Arterioscler Thromb. 1992;12:911-919.

- 7. Obarzanek E, Hunsberger SA, Van Horn L, et al.**
Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC).
Pediatrics. 1997;100:51-59.

- 8. Caggiula AW, Christakis G, Farrand M, et al, for the MRFIT Investigators.**
The Multiple Risk Intervention Trial (MRFIT). IV. Intervention on blood lipids.
Prev Med. 1981;10:443-475.

- 9. Zock PL, de Vries JH, Katan MB.**
Impact of myristic acid versus palmitic acid on serum lipid and lipoprotein levels in healthy women and men.
Arterioscler Thromb. 1994;14:567-575.

- 10. Denke MA, Grundy SM.**
Comparison of effects of lauric acid and palmitic acid on plasma lipids and lipoproteins.
Am J Clin Nutr. 1992;56:895-898.

- 11. Cater NB, Heller HJ, Denke M.**
Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans.
Am J Clin Nutr. 1997;65:41-45.

- 12. Bonanome A, Grundy SM.**
Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels.
N Engl J Med. 1988;318:1244-1248.

- 13. Mensink RP, Katan MB.**
Effects of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects.
N Engl J Med. 1990;323:439-445.

- 14. Grundy SM, Barrett-Connor E, Rudel LL, Miettinen T, Spector AA.**
Workshop on the impact of dietary cholesterol on plasma lipoproteins and atherogenesis.
Arteriosclerosis. 1988;8:95-101.

- 15. Mattson FH, Grundy SM.**
Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man.
J Lipid Res. 1985;26:194-202.

- 16. Grundy SM.**
Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol.
N Engl J Med. 1986;314:745-748.

- 17. Grundy SM.**
The optimal ratio of fat-to-carbohydrate in the diet.
Annu Rev Nutr. 1999;19:325-341.

- 18. US Department of Health and Human Services.**
Food and Drug Administration. Food labeling: health claims; soy protein and coronary heart disease: proposed rule.
Federal Register. 1998;63:62977-63015.

- 19. Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R; Stresa Workshop Participants.**
Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels.
Mayo Clin Proc. 2003;78:965-978.

- 20. Jenkins DJ, Kendall CW, Marchie A, et al.**
Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein.
JAMA. 2003;290:502-510.

Prevention of atherosclerotic cardiovascular disease - Grundy

21. Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.

JAMA. 2003;289:2560-2572.

22. Sacks FM, Svetkey LP, Vollmer WM, et al, for the DASH-Sodium Collaborative Research Group.

Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet.

N Engl J Med. 2001;344:3-10.

23. Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC.

Dietary intake of marine n-3 fatty acids, fish intake, and risk of coronary disease among men.

N Engl J Med. 1995;332:977-982.

24. Burr ML, Fehily AM, Gilbert JF, et al.

Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART).

Lancet. 1989;2:757-761.

25. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N.

Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.

Circulation. 1999;99:779-785.

26. Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M.

Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian Experiment of Infarct survival-4.

Cardiovasc Drugs Ther. 1997;11:485-491.

27. GISSI-Prevenzione Investigators.

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial.

Lancet. 1999;354:447-455.

28. Heart Protection Study Collaborative Group.

MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial.

Lancet. 2002;360:23-33.

29. Criqui MH.

Alcohol and coronary heart disease: consistent relationship and public health implications.

Clin Chim Acta. 1996;246:51-57.

30. Ridker PM, Wilson PW, Grundy SM.

Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk?

Circulation. 2004;109:2818-2825.

31. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute.

Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition.

Circulation. 2004;109:433-438.

32. Pearson TA, Blair SN, Daniels SR, et al.

AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee.

Circulation. 2002;106:388-391.

33. National Institutes of Health.

Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—The Evidence Report.

Obes Res. 1998;6(suppl 2):51S-209S.

34. US Department of Health and Human Services.

Physical activity and health: a report of the Surgeon General.

Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996:1-278.

What is the optimal macronutrient consumption for cardiovascular disease prevention?

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Dietary advice for preventing coronary heart disease (CHD) and type 2 diabetes has fluctuated considerably. Inability to substantiate evidence derived through epidemiology, use of surrogate biomarkers, and metabolic studies through randomized controlled trials is a major hindrance. Surveys of large populations have established eating patterns relating to the fewest and greatest rates of developing CHD. Clinical outcomes from consuming whole-grain cereals, cereal fiber, vegetables, fruits, fish, and unsaturated fats were in marked contrast to those of processed meats, high-fat dairy products, refined carbohydrates, fried foods, and sweets. This defined quantitative and qualitative criteria for macronutrients to combat CHD. Newer concepts of glycemic load and the increasing prevalence of the metabolic syndrome have led to reducing refined carbohydrates, emphasizing unsaturated and marine fatty acids, and substituting more protein to replace total fat.

Keywords: macronutrient; fat; carbohydrate; protein; fiber; coronary heart disease; glycemic load; obesity; metabolic syndrome

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The epidemic of coronary heart disease (CHD) that has been for decades the major cause of morbidity and mortality among the affluent populations of the world might well have been avoided had appropriate dietary and other lifestyle behavior been understood and implemented. The rapid and extensive spread of CHD, initially in “Western” countries during the 1960s, then through postwar eastern Europe, and more recently among Asians, testifies to the maladaptation of most populations to excess energy intake, especially from fat, together with smoking and lack of adequate energy expenditure. Equally impressive has been the decline in CHD incidence and mortality achieved through public health measures and medical management.

This review will evaluate the mix of macronutrients (fats, carbohydrates and protein) that might provide patterns of eating that have been associated in prospective and cross-sectional population studies with the least and the greatest rates of prevalence of CHD in Western populations. Whereas favorable and unfavorable patterns of consumption of foods have been shown with sufficient consistency to underpin valid public health messages, the amounts and types of required macronutrients remain in a perpetual state of flux. Since randomized controlled dietary intervention trials of the required scale are not feasible, the ev-

idence will not reach the consensus that is possible with trials of drugs. Nutritional science is therefore confounded by apparent changes in evidence so that the link between saturated fat consumption and CHD is being challenged, carbohydrates have shifted from being the foundation of an optimal diet to possibly contributing to disease, and higher consumption of protein is being strongly promoted.

Unlike essential micronutrients for which adequate intakes can be derived, thus quantifying their nutritional requirements, recommended macronutrient intakes are described as ranges. The AMDR (acceptable macronutrient distribution ranges) have been recently recommended by the Institute of Medicine (IOM) in the USA.¹ These are partly based on amounts considered optimal for

SELECTED ABBREVIATIONS AND ACRONYMS

AMDR	acceptable macronutrient distribution ranges
BMI	body mass index
DHA	docosahexaenoic acid
EPI	eicosapentaenoic acid
GI	glycemic index
IOM	Institute of Medicine
NHANES III	Third National and Nutrition Examination Survey
NHS	Nurses' Health Study

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preventing chronic diseases while ensuring adequate intakes of essential nutrients (Table I). However, acceptance has not been unanimous, and of possibly greater importance are the qualitative differences within each major class of macronutrients. Finally, recommendations about the optimal mix or percentage contributions of the macronutrients must take into account the translation into attractive and nutritious foods.

Much of nutritional science including the determination of AMDRs is focused on the effects on cardiovascular risk factors of individual nutrients and of nonnutrients widely distributed in the food supply. The evidence derives mainly from surrogates or biomarkers for the probability of future clinical CHD. While having differing degrees of robustness, biomarkers represent a logical and feasible advance in our understanding of the role of foods, nutrients, and supplements in diminishing the risk of CHD. Whereas AMDRs represent a basis for public health advice advances in the understanding of genetic factors and the interactions between nutrients and foods on the one hand, the increasing range of single nucleotide polymorphisms of regulating genes has raised prospects for “personalized or individualized health.”

OPTIMAL PATTERNS OF EATING FOR DIMINISHING CHD RISK

The consistency of findings in major prospective population studies defines a pattern of eating characterized by higher consumption of whole grains, fish, legumes, vegetables and fruit, low-fat dairy products, nuts, and unsaturated fats, which associates with least risk of CHD.² By contrast, in the same populations, consumption of red and processed meats, fats rich in either saturated

Fats	20%-35%
Carbohydrates	45%-65%
Protein	10%-35%

Table I. Acceptable macronutrient distribution range.¹

fat or *trans* fatty acids, fried foods, refined grains, and desserts and sweets was linked to the highest CHD risk (Table II). Hu et al³ have provided semiquantitative data on the likely reduction in CHD risk with various substitutions of dietary fats as well as of carbohydrate (Table III). The benefits of the prudent diet were independent of other lifestyle measures, although clearly augmented in the absence of smoking and increased physical activity. In the Nurses’ Health Study (NHS), the combination of a prudent diet, non-smoking, and regular exercise resulted in an 83% lesser risk of CHD compared with women in whom the corresponding risk factors were present.² In the same cohort of women, in whom there was a 31% decline in CHD incidence during 14 years of observation, improved pattern of eating contributed substantially. Among the macronutrients that showed significant change over this period, *trans* fat declined, while the consumption of cereal fiber, and marine n-3 fatty acids increased, as did the ratio of polyunsaturated to

saturated fat.⁴ In the United States Health Professionals’ Study of 44 875 men, followed for 8 years, a prudent pattern of eating comprising higher intakes of vegetables, fruit, whole grains, legumes, fish, and poultry was associated with substantially lower risk of future CHD compared with men eating the Western type American diet of French fries, high-fat dairy products, red and processed meats, refined grains, and sweets and desserts.²

Apart from these long-term prospective studies, analysis of the dietary patterns among 13 130 healthy adults in the Third National Health and Nutrition Examination Survey (NHANES III) showed that the Western pattern characterized by high intakes of red and processed meats, eggs and high-fat dairy products was associated with biomarkers of increased CHD risk.⁵ These included surrogate markers of insulin resistance (C-peptide, serum insulin, and glycated hemoglobin) that identify subjects with the metabolic syndrome. This survey also appears to have identified high carbohydrate consumption as a risk factor for the metabolic syndrome, at least in men. A higher risk of developing type 2 diabetes has also been attributed to the Western diet of red and processed meats, high-fat dairy products, French fries, and refined

Reduced risk	Increased risk
<ul style="list-style-type: none"> • Whole-grain cereals • Poultry • Low-fat dairy products • Fish • Unsaturated fats • Vegetables and fruits • Legumes • Nuts • Cereal fiber 	<ul style="list-style-type: none"> • Refined carbohydrate • Red and processed meats • Full-cream dairy products • Fried foods & French fries • <i>Trans</i> and saturated fats • Sweets • Desserts

Table II. Eating patterns that influenced CHD risk in prospective cohort studies.²⁻⁴



carbohydrates and sweets.⁶ Diabetes is of course a major risk factor for CHD.

MACRONUTRIENT CONSUMPTION AND CHD RISK

The healthy pattern of eating is a simple public health message. However, nutritionists and health authorities have focused on recommending diets on the basis of proportions

but not total fat, were components of the high-risk diet in the large prospective studies. A Cochrane report that systematically examined high-level evidence-based publications concluded cautiously that dietary saturated fat did raise the risk of CHD.⁷ By contrast, the progression of atherosclerosis measured by quantitative coronary angiography in a large group of postmenopausal women was recently reported to be less in those who ate relatively less

advice to reduce total fat consumption has been related to the potential disadvantages of increasing carbohydrate intake. The suggested IOM range of 20% to 35% energy from fat is linked to 45% to 65% energy from carbohydrate. Diets deriving <20% energy from fat and >65% from carbohydrate are likely to reduce the LDL cholesterol concentration, but raise plasma triglyceride and lower high-density lipoprotein (HDL) cholesterol.¹⁰ The latter combination of high triglyceride and low HDL cholesterol is the phenotype commonly occurring in the metabolic syndrome and insulin resistance that raises CHD risk. It is, however, also seen in populations eating little fat and much carbohydrate, as in Asian countries, where this lipoprotein phenotype does not appear to cause risk. However, provided the fat is predominantly monounsaturated and polyunsaturated and the carbohydrate unrefined, diets that are within the above ranges are unlikely to distort significantly the HDL cholesterol and triglyceride levels nor increase the risk of obesity and diabetes. The relationship of total fat consumption to developing obesity remains controversial, but given its energy value and metabolic propensity for storage, the suggested ceiling for fat intake of 35% seems reasonable.

The effects of individual fatty acids have been extensively researched, so that several meta-analyses have been reported with general consistency.¹¹ Equations have been computed for the estimation of the LDL cholesterol raising or lowering effects of individual fatty acids. In a meta-analysis of 60 controlled trials that examined the effects of individual fats and fatty acids on lipoprotein lipids, the total cholesterol-HDL cholesterol ratio as an index of risk was found to have changed little when carbohydrates replaced satu-

Substitution	Changed risk
Polyunsaturated for saturated fat (5% energy)	↓ 40%
Monounsaturated for saturated fat (5% energy)	↓ 40%
Unsaturated for <i>trans</i> fats (2% energy)	↓ 50%
Carbohydrates for saturated fat (5% energy)	↓ 15%
Carbohydrates for polyunsaturated fat (5% energy)	↑ 60%

Table III. Calculated approximate effect on CHD risk of substituting fats and carbohydrate (based on reference 3).

of the major macronutrients (fat, carbohydrate, and protein) expressed as percentages of total energy intake. Individual fatty acids and fiber can also be regarded as falling into the definition of AMDRs.

Dietary fat

The amounts and types of fats that constitute the least risk for CHD have been the foundation of recommended diets. The initial evidence came from comparisons of populations with very different patterns of fat consumption and from the large changes in dietary fat among migrating populations. In both circumstances, strong associations between fat consumption and CHD prevalence have been documented.² However, it has been more difficult to demonstrate such a linkage within Western populations in whom fat is a major component of the diet. Nevertheless, *trans* and saturated fats,

saturated fat and more carbohydrate, a finding that might be explained by an adverse response to dietary carbohydrate in subjects with the metabolic syndrome.⁸ However, the carbohydrate was mostly refined and there was no evidence that progression was related to total fat consumption. A conclusion might be that reducing fat should not be replaced with refined carbohydrate in the common disorder of the metabolic syndrome. The nutritional issues and the dietary management of the metabolic syndrome have been reviewed recently.⁹

The strongest evidence derives from the effects of fat and specific fatty acids on the major surrogate of future CHD, serum cholesterol, or low-density lipoprotein (LDL) cholesterol. However, changes in one macronutrient influence the proportions of the other macronutrients, and recent concern about the key

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rated fat, whereas substitution with *cis*-unsaturated fatty acids lowered the ratio significantly.¹⁰ *Trans* fats resulted in the highest ratio. Of individual saturated fatty acids, the increase in HDL cholesterol together with LDL cholesterol led to an actual decrease in the total cholesterol-HDL cholesterol ratio with lauric acid, no change with myristic and palmitic acids, and a slight decrease with stearic acid. Replacing fats with carbohydrate raised plasma triglyceride and led to the highest total cholesterol-HDL cholesterol ratio because of the reduction in HDL cholesterol despite a smaller reduction in LDL cholesterol. Replacing carbohydrate with polyunsaturated oils resulted in the lowest lipoprotein risk profile, resembling the marked difference in CHD risk in population studies (*Table III*).

Two comments are needed. First, the question of which lipoprotein phenotype influences CHD risk more: LDL cholesterol, which is generally lower when dietary fats are reduced, or HDL cholesterol, which is also reduced when carbohydrate replaces fat substantially. Both phenotypes are associated with increased CHD risk, although, given the large influence of genetic factors that determine individuals' responses to dietary change,¹² it is not certain, in the absence of randomized controlled intervention trials, that small changes in lipoprotein phenotypes increase risk. The second point is that high-fat diets have other deleterious effects on cardiovascular risk.¹¹ Thrombogenicity and endothelial dysfunction worsen after a high-fat meal, and insulin sensitivity probably deteriorates.

Although the reduction in LDL cholesterol is modest when monounsaturates, generally from olive oil, have been substituted for saturates, adverse metabolic changes such as

may occur with carbohydrates are avoided. Some Mediterranean populations consume up to 40% energy from fat mainly as olive oil and such diets have been reported to be associated with a lower prevalence of CHD.¹³

The suggested adequate intake for linoleic acid (18:2, n-6) is 5% to 10% energy, although considerably less is required for its essential fatty acid requirement. Dietary linoleic acid is part of the prudent, low-CHD risk pattern of eating that in prospective studies has diminished the incidence of CHD events; it is also the most potent LDL cholesterol-lowering fatty acid. Several controlled dietary intervention trials with large amounts of linoleic acid reduced the incidence of CHD events.^{2,14} Concerns about undesirable effects at 10% energy appear unfounded. At such an intake, there is little *in vivo* evidence for increased oxidant burden or significant *in vivo* interference with the conversion of α -linolenic acid (18:3, n-3) to eicosapentaenoic acid (EPA; 20:5, n-3).

The benefits of EPA and of DHA (docosahexaenoic acid [20:6, n-3]) on cardiovascular risk, predominantly on the prevention of sudden cardiac death, appear highly consistent.¹⁵ Initial evidence arose from fish-eating populations, although not all studies have confirmed the reduction in CHD risk among fish eaters. A meta-analysis has usefully demonstrated that eating more fish benefits people who had eaten little fish, but not habitual consumers of fish.¹⁶ In one of the few randomized clinical trials with a nutrient in which patients with CHD were given moderate amounts of EPA and DHA,¹⁷ sudden cardiac deaths were significantly lowered. The biological plausibility is strong: EPA and DHA reduce myocardial arrhythmogenic-

ity, correct endothelial dysfunction and arterial stiffness, improve the lipoprotein profile, and inhibit several key atherogenic processes.¹⁵

The major plant n-3 fatty acid, α -linolenic acid, may also reduce CHD risk independently of other fatty acids.² The suggested adequate intake for α -linolenic acid is between 1.1 and 1.6 g/d remembering that it is probably also an essential fatty acid, but the recommendation that EPA and DHA should comprise only 10% of total n-3 fatty acids is an underestimate for CHD prevention. Intakes of the marine n-3 fatty acids (EPA plus DHA) should be nearer 400 mg daily for healthy individuals, and on the basis of the secondary prevention trial, 1 g daily for patients with clinical CHD.¹⁷

Dietary carbohydrates

This macronutrient is undergoing a major revision in terms of the balance between its favorable and unfavorable effects on cardiovascular risk. Since dietary fat was regarded as the major contributor to CHD risk, less attention was paid to the amount and type of carbohydrate that might replace fat, and, as shown in *Table III*, substituting carbohydrate for saturated fat appears less effective than unsaturated fat substitutions. The concept of unrefined being preferable to refined carbohydrate, partly because of its greater fiber content, was considered adequate for public health advice. Indeed, starch-rich foods such as whole-grain cereal, vegetables, legumes, and fruits were prominent within the low-CHD-risk group of foods.²⁻⁴ Consumption of whole-grain cereals and of cereal fiber¹⁸ has been confirmed in numerous population studies to independently predict reduced CHD risk. By contrast, the increased consumption of refined carbohydrates in the United



States during the 20th century is positively correlated with the prevalence of type 2 diabetes.¹⁹

Metabolic explanations for the beneficial effects of eating whole-grain cereals include improved insulin sensitivity, especially in overweight subjects, diminished prevalence of overweight itself, and the rich micronutrient content of the bran that includes antioxidants and folate.

It is critical to public health policy to recognize that these key observations have not been negated by the controversy over carbohydrates. What has changed is the recognition that, as in the case of fats, carbohydrates need to be redefined in qualitative terms. The concept of rapidly and slowly digestible and absorbable carbohydrates is not new, and the term resistant starch has been applied to the latter form of starch reflecting structure and chemical composition, such as higher amylose content, which contributes to slower digestion. Slowly digestible starch results in diminished rate of glycemia, requiring a smaller insulin response. In an environment of obesity and the metabolic syndrome characterized by insulin resistance, carbohydrates that elicit lower insulin secretion are likely to preserve pancreatic islet cell function and delay conversion to diabetes.

That concept has led to classification of carbohydrates, comprising both starch and simple sugars as having a high or low glycemic index (GI) based on the rise of blood glucose following a meal.²⁰ The index alone does not take into account the amount of high GI foods that may confer increased risk for CHD and type 2 diabetes. That has led to the term of glycemic load, which is the product of the GI times the amount of carbohydrate load, and has been

shown to be predictive for future diabetes,²⁰ although possibly only in people with a family history of diabetes or low-energy expenditure.²¹ In the Framingham Offspring Study the prevalence of the metabolic syndrome was greater in those eating high GI foods even after accounting for body mass index (BMI).²² In this context, the GI concept is useful. However, other studies have not confirmed the link between GI or glycemic load and future diabetes or CHD, and this area remains controversial.

Unease about the GI concept includes concern that some foods that contain sugar and fats have a relatively low GI value, yet might seem intuitively undesirable. Furthermore, not all nutritionists are convinced that potatoes, rice, and white bread should be avoided by people at risk for insulin resistance because of their relatively high GI. That they should contribute less to the total glycemic load than lower GI foods such as whole-grain cereals, fibrous vegetables, and legumes in diets for insulin-resistant subjects differs little from past advice. For subjects with the metabolic syndrome, an overall reduction in carbohydrate intake and substitution with higher protein foods and monounsaturated fats seems appropriate.

The obsession with unusual weight-loss diets has added to the unfortunate concept of "bad carbohydrates" and recommendations for substantial reduction in the AMDR for carbohydrates that currently stands at 45% to 65 % energy.¹ The marked reduction in carbohydrates has led to proportionately more protein and fat, up to 40% as protein. These diets undoubtedly result in short-term weight loss that exceeds conventional balanced overall reduction in energy.²³ However, studies over 1 year cannot distinguish between the

eventual weight loss from most energy reduced diets. A major public health concern about the very-low-carbohydrate diets is less about safety (which is marginal) than that the hard facts about the protective benefits of whole-grain and other slowly digestible carbohydrates will be lost.

Dietary fiber or nonstarch polysaccharide also clearly reduces CHD risk, especially as part of a prudent diet as discussed above, and has been documented in a recent meta-analysis.²⁴ Both "insoluble" fiber such as that in cereals and "soluble" fiber (beta-glucans, psyllium, pectin, etc) reduce risk factors such as postprandial glycemia and LDL cholesterol. The Food and Drug Administration (FDA) has given qualified support for the inclusion of soluble nonstarch polysaccharides within diets that may reduce the risk of CHD.

Dietary protein

It is self-evident that the AMDR for protein will depend on the proportions of energy allocated to fat and carbohydrate. A range of 10% to 25% appears rational, although there has been a trend to higher values. In severely energy-reduced weight-loss diets, the protein content may reach 40%, reflecting limitations in carbohydrates and fat. Modeling of such diets suggests that 40% may be required for adequate micronutrients such as iron and zinc. During weight loss, lean body mass, bone mineralization, and insulin sensitivity are better maintained when protein intake is high.²³ The success of such diets may reflect the satiating effects of protein.

Earlier concerns that high protein intake may lead to bone demineralization and even to renal impairment have not been confirmed.

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Qualitative differences in protein reflecting amino acid content are well known. Recent interest in soy protein as potentially superior to animal protein within diets to reduce the risk of CHD has recently received FDA support. The claim is based on the perceived effect of soy protein on LDL cholesterol. However, several editorials have expressed uncertainty about the importance of the minor reductions in LDL cholesterol, which have not been consistently observed.²⁵

REFERENCES

1. IOM (Institute of Medicine).

Dietary Reference Intakes: Application in Dietary Assessment. Washington DC: National Academy Press; 2000.

2. Hu FB, Willett WC.

Optimal diets for prevention of coronary heart disease.

JAMA. 2002;288:2569-2578.

3. Hu FB, Stampfer MJ, Manson JE, et al.

Dietary fat intake and the risk of coronary heart disease in women.

N Engl J Med. 1997;337:1491-1499.

4. Hu FB, Stampfer MD, Manson JA, et al.

Trends in the incidence of coronary heart disease and changes in diet and lifestyle in women.

N Engl J Med. 2000;343:530-537.

5. Kerver JM, Yang EJ, Bianchi L, Song WO.

Dietary patterns associated with risk factors for cardiovascular disease in healthy US adults.

Am J Clin Nutr. 2003;78:1103-1110.

6. Van Dam RB, Rimm EB, Willett WC, Stampfer MD, Hu FB.

Dietary patterns and risk for Type 2 diabetes mellitus in US men.

Ann Int Med. 2002;136:201-209.

7. Hooper L.

Dietetic guidelines: diet in secondary prevention of cardiovascular disease.

J Hum Nutr Diet. 2001;14:297-305.

8. Knopp RH, Retzlaff BM.

Saturated fat prevents coronary artery disease? An American paradox.

Am J Clin Nutr. 2004;80:1102-1103.

9. Nestel PJ.

Nutritional aspects in the causation and management of the metabolic syndrome.

Endocrinol Metab Clin N Am. 2004;33:483-492.

10. Mensink RP, Zock PL, Katan MB.

Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials.

Am J Clin Nutr. 2003;77:1146-1155.

11. Nestel PJ.

Serum and trans fatty acids and coronary heart disease.

Eur Heart J. 1999;1(suppl S):S19-S23.

12. Ordovas JM.

Cardiovascular disease genetics: a long and winding road.

Curr Opin Lipidol. 2003;14:47-54.

13. Rimm MB, Stampfer MJ.

Diet, lifestyle and longevity—the next steps?

JAMA. 2004;292:1490-1492.

14. Kris-Etherton PM, Hecker KD, Binkoski AE.

Polyunsaturated fatty acids and cardiovascular health.

Nutr Rev. 2004;62:414-426.

15. Harris WS, Park Y, Isley WL.

Cardiovascular disease and long-chain omega-3 fatty acids.

Curr Opin Lipidol. 2003;14:9-14.

16. Marckman P, Gronbaek M.

Fish consumption and coronary heart disease mortality. A systematic review of prospective cohort studies.

Eur J Clin Nutr. 1999;53:585-590.

17. GISSI-Prevenzione Investigators.

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial.

Lancet. 1999;354:447-455.

18. Wolk AJ, Manson JE, Stampfer MJ, et al.

Long-term intake of dietary fiber and decreased risk of coronary heart disease among women.

JAMA. 1999;281:1998-2004.



19. Gross LS, Li L, Ford ES, Liu S.

Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: an ecological assessment.

Am J Clin Nutr. 2004;79:774-779.

20. Brand-Miller JC.

Glycemic load and chronic disease.

Nutr Rev. 2003;61(5 pt 2):S49-S55.

21. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB.

Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women.

Am J Clin Nutr. 2004;80:348-356.

22. McKeown NM, Meigs JB, Liu S, Saltzman E, Wilson PW, Jacques PF.

Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort.

Diabetes Care. 2004;27:538-546.

23. Noakes M, Clifton P.

Weight loss, diet composition and cardiovascular risk.

Curr Opin Lipidol. 2004;15:31-35.

24. Pereira MA, O'Reilly E, Augustsson K, et al.

Dietary fiber and risk of coronary heart disease: a pooled analysis of cohort studies.

Arch Int Med. 2004;164:3760-3376.

25. Nestel PJ.

Role of soy protein in cholesterol-lowering: how good is it?

Arterioscler Thromb Vasc Biol. 2002;22:1743-1745.

What is the current view of the role of stress in the causation of CAD?

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The popular belief that stress causes coronary events is now supported by many studies that have carefully excluded self-reporting bias, whether by monitoring post-bereavement mortality rates, increased episodes of ventricular tachycardia in patients with implantable cardioverter-defibrillators in response to natural disaster, or more recently, the reversible perfusion defects measured by single photon emission computed tomography (SPECT) in response to mental stressor administration in the laboratory. Indeed, mental stress ischemia may better predict ischemia during Holter monitoring than ischemia during exercise; it is also associated with a 3-fold relative increase in mortality rate. On that basis, mental stress testing could be effective in selecting at-risk patients for appropriate intervention.

Nontraditional risk factors for coronary artery disease have been under study for a number of years. Recently, psychosocial factors influencing heart disease have been recognized as important in the prevention, development, and treatment of coronary artery disease (CAD).¹ The INTERHEART study recently reported that 28.8% of acute myocardial infarctions are attributed to psychosocial factors (*Figure 1*).² Because psychosocial stress may be a modifiable risk factor, it is important to understand its pathological effect on the cardiovascular system. In this paper, we will review the pathophysiology, epidemiology, and clinical importance of acute and chronic stress on the development of cardiovascular disease.

ACUTE STRESS

For many years there has been anecdotal evidence that stressful events precipitate coronary events. That extreme anger or excitement leads to heart attacks has become a part of common belief. In recent years, evidence-based research has begun to support these beliefs. A case-crossover analysis of anger as a trigger of myocardial infarction (MI) was reported by Möller et al in 1999.³ They found that up to an hour after an episode of anger, the relative risk of MI was 9.0 (95% CI, 4.4-18.2). The Multicenter Investiga-

tion of the Limitations of Infarct Size (MILIS) study found that emotional upset was the most often reported trigger of an acute MI.⁴ Other studies point to anger as a trigger of myocardial infarction⁵ or to arrhythmias in patients with implantable cardioverter defibrillators.⁶ These studies may be identifying lifestyle factors that contribute to the overall risk of acute MI.

Some researchers have criticized these studies stating that the results are subject to biased recall. They feel that subjects who experience an MI are more likely to report an inciting emotion or event. However, other studies of an epidemiological nature support these conclusions. Three studies have evaluated the effects of naturally occurring environmental stressors such as war or documented natural disasters. After the 1994 Northridge earthquake, the number of episodes of ventricular tachycardia or fibrillation increased among patients with implantable cardioverter-defibrillators.⁷

Personal tragedy has also been associated with increased mortality due to ischemic heart disease. A study conducted by Kaprio and colleagues found that the relative mortality risk after the death of a loved one was highest among those with preexisting ischemic heart disease. This increased relative risk returned

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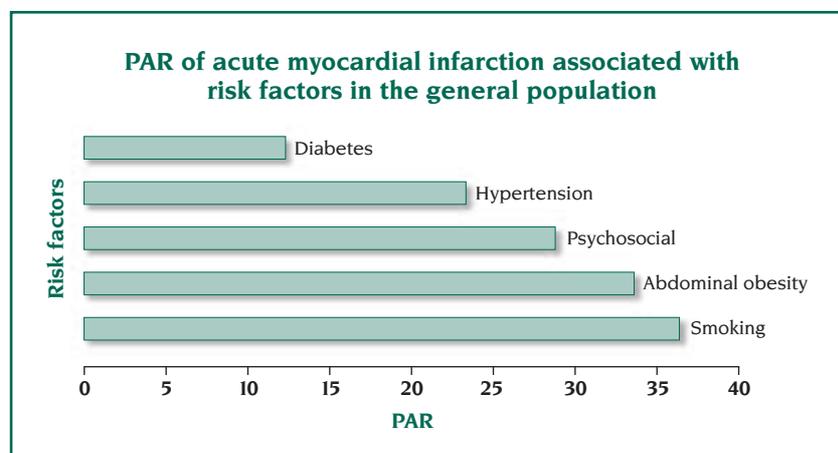


Figure 1. Comparison of psychosocial risk to other major risk factors for acute myocardial infarction. PAR, population attributable risk.

Modified from reference 2: Yusuf S, Hawken S, Ounpuu S, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937-52 (Table 3). Copyright © 2004, Elsevier Ltd.

to normal population levels 1 month following bereavement.⁸ Other studies examine man-made rather than natural events. A recent study investigated the health-related effects of the 9/11 terrorist attacks in places distant from New York City. Shedd et al reported that 132 patients in a Florida hospital had a 2.8% increase in the frequency of ventricular arrhythmias requiring implantable cardioverter-defibrillator treatment in the 30-day period after the attacks compared with the 30 days before the attacks.⁹ These results are similar to the ones reported in a New York study in 2004.¹⁰ These studies support the belief that psychological stress may be an inciting factor in the onset of cardiac events.

CHRONIC STRESS

Death and illness occurring after coronary events is associated with traditional risk factors as well as low socioeconomic status (SES), poor nutrition, and poor mental and physical health.¹¹ Chronic stress may be a common factor linking socioeconomic and mental health status to coronary artery disease.

Socioeconomic factors

Although poor nutrition, access to medical care, and exercise habits have long been thought of as the way low SES affects health,¹¹ researchers are now finding that these traditional risk factors do not tell the whole story. A person's occupation, wealth, social power, and education combine to make up a person's socioeconomic status. Together, these are major predictors of cardiovascular health.¹²

Occupational factors

Over the past 20 years, researchers have discovered a connection between occupational factors such as job satisfaction and autonomy to the risk of developing coronary disease. A study by Karasek et al in 1988 found that men who worked in psychologically demanding jobs with little decision-making authority experienced more myocardial infarctions even when controlling for age, race, education, systolic blood pressure, serum cholesterol, and physical exertion.¹³ In contrast, some studies find that job demands,

job strain, and social support are not associated with a higher prevalence of MI, but that low job control is associated with increased risk of cardiac events.¹⁴ Currently, it is unknown whether the risk of cardiovascular disease increases sharply after some threshold of stress intensity and duration or if the relationship is graded.¹²

Gender

While lack of autonomy on the job has been associated with increased cardiac risk in men, this association is not as strong in women. The Stockholm Female Coronary Risk Study found that occupational status rather than job control is a stronger predictor of cardiac risk in women.¹⁵ However, more studies in women need to be conducted.

Other studies have examined the impact of occupation and marital stress on the development of depression in women with CAD. Two such studies found that risk of developing depression increased incrementally with marital stress, but not with work-related stress. They also found that women with CAD were twice as likely to develop depression as those who were healthy.^{16,17}

Physical health

Obesity has been associated with hypertension,^{18,19} insulin resistance,²⁰ and dyslipidemia.¹⁹ Together these are referred to as "the metabolic syndrome."²¹ A model proposed by Vitaliano et al²² proposes that possessing few personal resources and high personal vulnerabilities in combination with chronic stress leads to distress. This state of distress encourages poor health habits that may lead to the metabolic syndrome.²² This syndrome has proven to be a predictor for the development of cardiovascular disease.²⁰

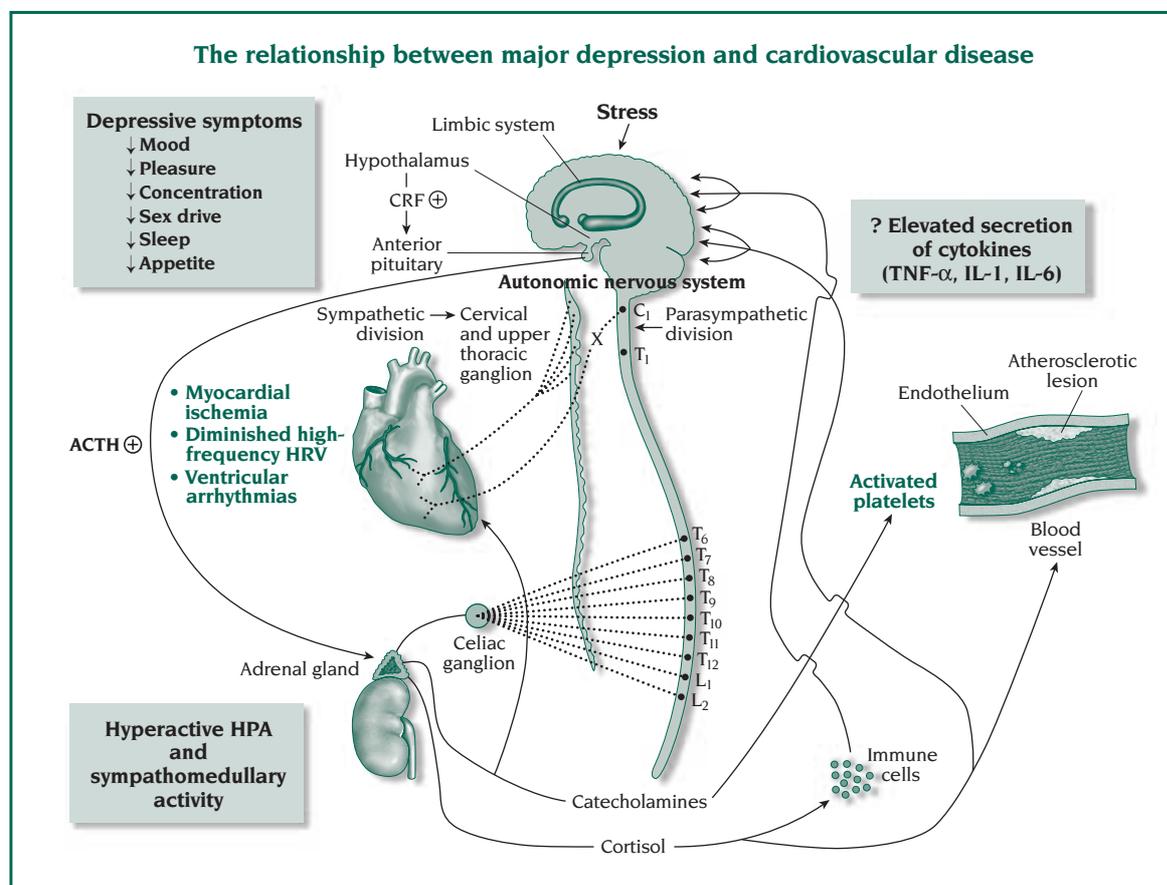


Figure 2. Hypothetical schema of pathophysiological alterations associated with depression that likely contribute to increased vulnerability to cardiovascular disease (CVD). Autonomic nervous system innervation of the heart via parasympathetic vagus (X) and sympathetic (post-ganglionic efferents from cervical and upper-thoracic paravertebral ganglia) nerves is shown.

Abbreviations: ACTH, corticotropin; CRF indicates corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenocortical axis; HRV, heart rate variability; IL-1, interleukin 1; IL-6, interleukin 6; TNF, tumor necrosis factor.

Modified from reference 23: Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry. 1998;55:580-592. Copyright © 1998, JAMA & Archives.

Depression

Numerous studies have reported an association between CAD and depression (Figure 2).²³ Clinical depression includes symptoms such as anhedonia, fatigue, and depressed mood as well as eating and sleeping disturbances. The prevalence of major depression in patients with a past history of MI is reported to be as high as 23%.²⁴ One study found that patients with cardiovascular disease who met the criteria for major depression were 2.5 times more likely to develop a serious cardiac complication over the next 12 months than nondepressed patients.²⁵

Hostility

Hostile individuals have a higher risk of developing coronary heart disease and premature death than less hostile individuals.^{26,27} Several mechanisms have been suggested, including exaggerated sympathetic nervous system response to stress, low social support, smoking, and obesity.²⁸⁻³⁰ Some research points to a role for β -adrenergic receptor function in the relationship between hostility and CAD. The increased chronic stress levels experienced by hostile individuals may lead to an eventual downregulation of norepinephrine receptors. Reduced

cardiac β -adrenergic receptor responsiveness has been associated with hypertension, ischemic heart disease, and congestive heart failure.³¹⁻³⁵

LABORATORY-INDUCED MENTAL STRESS ISCHEMIA

People experience emotional stress on a daily basis in response to interpersonal conflict and internal perception of events. Several methods have been developed to recreate stressful events in a controlled laboratory setting. Methods such as the Stroop color word task and



mental arithmetic create stress by making the patient attempt to keep up with an increasingly difficult mental task. Anger recall and public speaking require the patient to remember or imagine a situation of conflict and confrontation with a difficult person or situation. In the laboratory setting, 40% to 70% of patients with coronary artery disease experience ischemia in response to mental stressors.³⁶

Just as there are various methods of inducing mental stress there are many ways of detecting the resultant ischemia. Over the years imaging tools such as radionuclide ventriculography (RVG) for ejection fraction, positron emission tomography (PET), echocardiography for wall motion, and single photon emission computed tomography (SPECT) imaging for reversible perfusion defects have been used. Earlier studies made use of RVG and PET, but due to high cost and low availability newer methods are now employed. SPECT has been used in recent years to detect perfusion changes induced by mental stress with high sensitivity, specificity, and reproducibility.³⁶

While mental stress studies are not yet clinically utilized, the use of these tools has helped to build evidence that the heart's reaction to laboratory mental stress has serious prognostic consequences in patients with and without preexisting cardiovascular disease. Sheps et al reported in 2002 that patients who develop cardiac ischemia in response to mental stress have a 3-fold relative increase in mortality rate compared with those who do not develop mental stress ischemia.³⁷

PATHOPHYSIOLOGY

The physiologic response to mental stress includes changes in heart rate, blood pressure, and peripheral re-

sistance. A recent study by Strike et al³⁸ found that in comparison with healthy controls, patients with CAD have a greater increase in systolic blood pressure and heart rate during mental stress. They also found that the increases in heart rate corresponded with higher subjective stress and depression scores.

Certain hemodynamic changes imply that the physiology of mental stress-induced ischemia is different from that of exercise-induced ischemia. Because of the lower heart rate that is present during mental stress testing compared with exercise stress testing, some researchers believe that episodes of mental stress ischemia display a different balance between cardiac supply and demand than that induced by exercise.³⁹ Some studies reveal that although the cardiac demand may be lower, the cardiac supply may be decreased due to coronary constriction or dysfunction of the myocardial microcirculation.^{40,41}

Recent studies report that the presence of mental stress ischemia is a better predictor of having ischemia during Holter monitoring than during exercise. Because most ambulatory ischemic events occur at relatively low heart rates and during rest or light physical activities,³⁹ it better simulates the silent ischemia brought on by daily stress. The clinical implication is that mental stress testing may be an effective tool in identifying those patients who experience mental stress ischemia during their daily lives.

In contrast to the gradual increase in intensity seen with physical exercise, mental stress is introduced suddenly. In fact, the maximal hemodynamic changes in mental stress testing are observed close to the onset of the stressor.⁴² The endothelial vessel wall experiences an in-

crease in shear stress with sudden increases in heart rate and blood pressure. These hemodynamic forces stimulate endothelial nitric oxide and prostaglandin I₂ release. In arteries affected by cardiovascular disease nitric oxide and prostaglandin release is decreased. This increases susceptibility to platelet adhesion and aggregation.⁴³ Therefore, hemodynamic and thrombogenic responses to mental stress may increase the likelihood of cardiac events in patients with CAD.

Autonomic control of the heart rate, measured as heart rate variability, supplies information about the relative balance of sympathetic and parasympathetic tone. Some studies suggest that depressed patients exhibit parasympathetic withdrawal, which manifests as decreased heart rate variability.⁴⁴ Because depressed patients tend to have low heart rate variability,⁴⁴ they are more susceptible to malignant cardiac arrhythmias and sudden death.⁴⁵

Atherosclerosis is central to the development of acute MI. Any process that accelerates plaque or thrombus formation is an important risk factor for acute coronary syndrome. The normal cardiovascular system has safeguards in place to prevent excessive thrombus formation.⁴⁶ However, certain nontraditional risk factors may moderate intrinsic antithrombotic activity. For example, one study reports a lower platelet-aggregating time and higher levels of platelet factor 4 and β -thromboglobulin in angina patients than in healthy controls subject to mental stress.⁴⁷

TREATMENT OPTIONS

A variety of intervention trials have attempted to find a relationship between participation in a stress-reducing intervention and incidence

What is the role of stress in the causation of CAD? - Pusey and others

of adverse clinical events. Past intervention methods have included cognitive therapy, support groups, and meditation. The Enhancing Recovery in Coronary Heart Disease Trial⁴⁸ examined whether treating depression and low social support early after an acute MI would reduce death and recurrent nonfatal infarctions. They reported that post-MI patients receiving cognitive-behavioral treatment did not have lower survival rates at 6 months than post-MI patients who did not receive therapy. Because there are so few studies examining the effects of psychological treatment on cardiovascular disease, more work needs to be done in this area before any conclusions can be drawn.

REFERENCES

- 1. US Department of Health and Human Services.**
National Heart, Lung, and Blood Institute Report of the Task Force on Behavioral Research in Cardiovascular, Lung, and Blood Health and Disease.
Available at: <http://www.nhlbi.nih.gov/resources/docs/taskforce.htm>. 1998.
- 2. Yusuf S, Hawken S, Ounpuu S, et al.**
Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study.
Lancet. 2004;364:937-952.
- 3. Möller J, Hallqvist J, Diderichsen F, et al.**
Do episodes of anger trigger myocardial infarction? A case-crossover analysis in the Stockholm Heart Epidemiology Program SHEEP.
Psychosom Med. 1991;61:842-849.
- 4. Tofler GH, Stone PH, Maclure M.**
Analysis of possible triggers of acute myocardial infarction (the MILIS Study).
Am J Cardiol. 1990;66:22-27.
- 5. Mittleman MA, Maclure M, Sherwood JB.**
Triggering of acute myocardial infarction onset by episodes of anger. Determinants of Myocardial Infarction Onset Study Investigators.
Circulation. 1995;92:1720-1725.
- 6. Lampert R, Joska T, Burg MM.**
Emotional and physical precipitants of ventricular arrhythmia.
Circulation. 2002;106:1800-1805.
- 7. Nishimoto Y, Firth BR, Kloner RA.**
The 1994 Northridge earthquake triggered shocks from implantable cardioverter defibrillators.
Circulation. 1995;92(suppl I):I606.
- 8. Kaprio J, Koskenvuo M, Rita H.**
Mortality after bereavement: a prospective study of 95,647 persons.
Am J Public Health. 1987;77:283-287.
- 9. Shedd OL, Sears SF Jr, Harvill JL, et al.**
The World Trade Center attack: increased frequency of defibrillator shocks for ventricular arrhythmias in patients living remotely from New York City.
J Am Coll Cardiol. 2004;44:1265-1267.
- 10. Steinberg JS, Arshad A, Kowalski M, et al.**
Increased incidence of life-threatening ventricular arrhythmias in implantable defibrillator patients after the World Trade Center attack.
J Am Coll Cardiol. 2004;44:1261.
- 11. Kaplan GA, Keil JE.**
Socioeconomic factors and cardiovascular disease: a review of the literature.
Circulation. 1993;88:1973-1998.
- 12. Krantz DS, McCeney M.**
Effects of psychological and social factors on organic disease: a critical assessment of research on coronary heart disease.
Annu Rev Psychol. 2002;53:341-369.
- 13. Karasek RA, Theorell T, Schwartz JE, et al.**
Job characteristics in relation to the prevalence of myocardial infarction in the US Health Examination Survey (HES) and the Health and Nutrition Examination Survey (HANES).
Am J Public Health. 1988;78:910-918.
- 14. Bosma H, Marmot MG, Hemingway H, et al.**
Low job control and risk of coronary heart disease in Whitehall II (prospective cohort) study.
BMJ. 1997;314:558-565.
- 15. Wamala SP, Mittleman MA, Horsten M, et al.**
Job stress and the occupational gradient in coronary heart disease risk in women. The Stockholm Female Coronary Risk Study.
Soc Sci Med. 2000;51:481-489.
- 16. Balog P, Janszky I, Leineweber C, et al.**
Depressive symptoms in relation to marital and work stress in women with and without coronary heart disease. The Stockholm Female Coronary Risk Study.
J Psychosom Res. 2003;54:113-119.
- 17. Orth-Gomer K, Wamala SP, Horsten M, et al.**
Marital stress worsens prognosis in women with coronary heart disease: the Stockholm Female Coronary Risk Study.
JAMA. 2000;284:3008-3014.
- 18. Barrett-Conner E.**
Obesity, hypertension and stroke.
Clin Exp Hypertens. 1990;12:769-782.
- 19. Modan M, Halkin H.**
Hyperinsulinemia or increased sympathetic drive as link for obesity and hypertension.
Diabetes Care. 1991;14:470-487.
- 20. Schneiderman N, Skyler JS.**
Insulin metabolism, sympathetic nervous system regulation, and coronary heart disease prevention. In: Orth-Gomer K, Schneiderman N, eds.
Behavioral Medicine Approaches to Cardiovascular Disease Prevention. Hildale, NJ: Lawrence Erlbaum; 1995.
- 21. Bjorntorp P.**
Abdominal obesity and the metabolic syndrome.
Ann Med. 1992;24:465-468.
- 22. Vitaliano P, Scanlan J, Zhang J, et al.**
A path model of chronic stress, the metabolic syndrome, and coronary heart disease.
Psychosom Med. 2002;64:418-435.



23. Musselman DL, Evans DL, Nemeroff CB.

The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment.

Arch Gen Psychiatry. 1998;55:580-592.

24. Glassman A, O'Connor C, Califf R, et al.

Sertraline treatment of major depression in patients with acute MI or unstable angina.

JAMA. 2002;288:701-709.

25. Carney RM, Rich MW, Freedland KE, et al.

Major depressive disorder predicts cardiac events in patients with coronary artery disease.

Psychosom Med. 1988;50:627-633.

26. Barefoot JC, Dahlstrom WG, Williams RB Jr.

Hostility CHD, incidence, and total mortality: a 25-year follow-up study of 255 physicians.

Psychosom Med. 1983;45:59.

27. Knox SS, Siegmund KD, Weidner G, et al.

Hostility, social support, and coronary heart disease in the National Heart, Lung, and Blood Institute Family Heart Study.

Am J Cardiol. 1998;82:1192-1196.

28. Smith TW.

Hostility and health: current status of a psychosomatic hypothesis.

Health Psychol. 1992;11:139-150.

29. Suarez EC, Kuhn CM, Schanberg SM, et al.

Neuroendocrine, cardiovascular, and emotional responses of hostile men: the role of interpersonal challenge.

Psychosom Med. 1998;60:78-88.

30. Allen J, Markovitz J, Jacobs DR Jr, Knox SS.

Social support and health behavior in hostile black and white men and women in CARDIA. Coronary artery risk development in young adults.

Psychosom Med. 2001;63:609-618.

31. Bertel O, Buhler FR, Kiowski W, Lutold BF.

Decreased beta-adrenoreceptor responsiveness as related to age, blood pressure, and plasma catecholamines in patients with essential hypertension.

Hypertension. 1980;2:130-138.

32. Dhalla NS, Dixon IM, Rupp H, Barninsky J.

Experimental congestive heart failure due to myocardial infarction: sarcolemmal receptors and cation transporters.

Basic Res Cardiol. 1991;86(suppl 23):13-23.

33. Brodde OE.

Beta-adrenoceptors in cardiac disease.

Pharmacol Ther. 1993;60:405-430.

34. Lefkowitz RJ, Rockman HA, Koch WJ.

Catecholamines, cardiac beta-adrenergic receptors, and heart failure.

Circulation. 2000;101:1634-1637.

35. Suarez EC, Shiller AD, Kuhn CM, et al.

The relationship between hostility and beta-adrenergic receptor physiology in healthy young males.

Psychosom Med. 1997;59:481-487.

36. Kim CK, Bartholomew BA, Mastin ST.

Detection and reproducibility of mental stress-induced myocardial ischemia with Tc-99m sestamibi SPECT in normal and coronary artery disease populations.

J Nucl Cardiol. 2003;10:56-62.

37. Sheps DS, McMahon RP, Becker L, et al.

Mental stress-induced ischemia and all-cause mortality in patients with coronary artery disease: Results from the Psychophysiological Investigations of Myocardial Ischemia study.

Circulation. 2002;105:1780-1704.

38. Strike PC, Magid K, Brydon L, et al.

Exaggerated platelet and hemodynamic reactivity to mental stress in men with coronary artery disease.

Psychosom Med. 2004;66:492-500.

39. Blumenthal JA, Jiang W, Waugh RA, et al.

Mental stress-induced ischemia in the laboratory and ambulatory ischemia during daily life: association and hemodynamic features.

Circulation. 1995;92:2102-2108.

40. Lacy CR, Contrada RJ, Robbins ML, et al.

Coronary vasoconstriction induced by mental stress (simulated public speaking).

Am J Cardiol. 1995;75:503-505.

41. Dakak N, Quyyumi AA, Eisenhofer G, et al.

Sympathetically mediated effects of mental stress on the cardiac microcirculation of patients with coronary artery disease.

Am J Cardiol. 1995;76:125-130.

42. Rozanski A, Blumenthal JA, Kaplan J.

Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy.

Circulation. 1999;99:2192-2217.

43. Selwyn AP.

Prothrombotic and anti-thrombotic pathways in acute coronary syndromes.

Am J Cardiol. 2003;91(suppl):3H-11H.

44. Stein PK, Carney RM, Freedland KE, et al.

Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease.

J Psychosom Res. 2000;48:493-500.

45. Gorman JM, Sloan RP.

Heart Rate variability in depressive and anxiety disorders.

Am Heart J. 2000;140(suppl 4):77-83.

46. Libby P.

Current concepts of the pathogenesis of the acute coronary syndromes.

Circulation. 2001;104:365-372.

47. Wallen NH, Held C, Rehnqvist N, et al.

Effects of mental and physical stress on platelet function in patients with stable angina pectoris and healthy control.

Eur Heart J. 1997;18:807-815.

48. Jiang WA, Blumenthal JA.

Depression and ischemic heart disease: overview of the evidence and treatment implications.

Curr Psychiatr Rep. 2003;5:47-54.

What do you recommend for individual patients and the general public about consumption of alcohol? Do the benefits outweigh the risks?

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Extensive research suggests that moderate alcohol consumption lowers the risk of atherosclerotic cardiovascular disease (CVD) by 20%. However, this benefit requires serious qualification: it does not cover nonatherosclerotic CVD; it applies to no more than two drinks daily in men and one in women; it is confined to those aged 60 and over with, or at increased risk of, atherosclerotic CVD; and even in this category, it is not so clear-cut as to warrant recommending therapeutic use of alcohol in abstainers. Elsewhere, in the population at large, the benefit-risk ratio even in strictly medical terms is resoundingly negative, notably in women, due to greater bioavailability and the dose-response association with breast cancer, and in younger adults in whom any level of alcohol consumption may increase coronary calcification.

Keywords: alcohol; abuse; epidemiology; guideline; cardiovascular disease; atherosclerosis; observational study; cardioprotection

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The title of this paper poses three separate questions: recommendations to the individual patient, recommendations to the general public, and the risk-benefit ratio. Answering these questions first requires a focused view of the research in this area. We will review observational studies, experimental studies, and address the implications for the individual patient and the general public separately.

OBSERVATIONAL STUDIES

The large body of research on the relation of alcohol consumption to cardiovascular disease (CVD) has produced reasonably consistent results. First, moderate consumption of alcohol, defined as 1 to 2 drinks per day, is associated with a reduced risk of CVD from atherosclerotic causes, in particular coronary heart disease, stroke, and peripheral arterial disease.¹⁻³ Although individual studies show considerable variation, this risk reduction averages around 20%. Despite widespread opinion to the contrary, studies within defined populations show that the effect size does not differ for red wine, white wine, beer, or spirits.⁴ However, the apparently greater benefit for wine in ecologic studies across populations⁵ suggests that the differential manner in which

wine is consumed compared with other alcoholic beverages (sipped, with meals) may be a healthier way to consume alcohol.⁶ It is important to note that consumption of alcohol is not protective for nonatherosclerotic cardiovascular diseases, such as arrhythmias, cardiomyopathy, and hemorrhagic stroke. In fact, alcohol, especially at higher doses, but even in moderate doses, may lead to or exacerbate the latter conditions.⁷

Second, alcohol consumption at levels beyond 2 drinks per day does not produce additional benefit. In fact, consumption at higher levels in several studies is typically associated with increased cardiovascular risk and virtually always associated with increased risk of several non-CVD end points, including liver disease, cancer, accidents, and violence.⁸ In addition, total mortality begins to increase sharply at more than 2 drinks per day. Thus, there is a U-shaped relationship between alcohol consumption and both total cardiovascular and noncardiovascular outcomes. This is illustrated by *Figure 1*, from a prospective study of 276 802 men followed for 12 years.⁸ Although there is some benefit for coronary mortality even at higher levels of drinking, it is clear that the full benefit is achieved at a single drink per day. Above two drinks per day, mortality from other causes, including cerebrovascular disease,

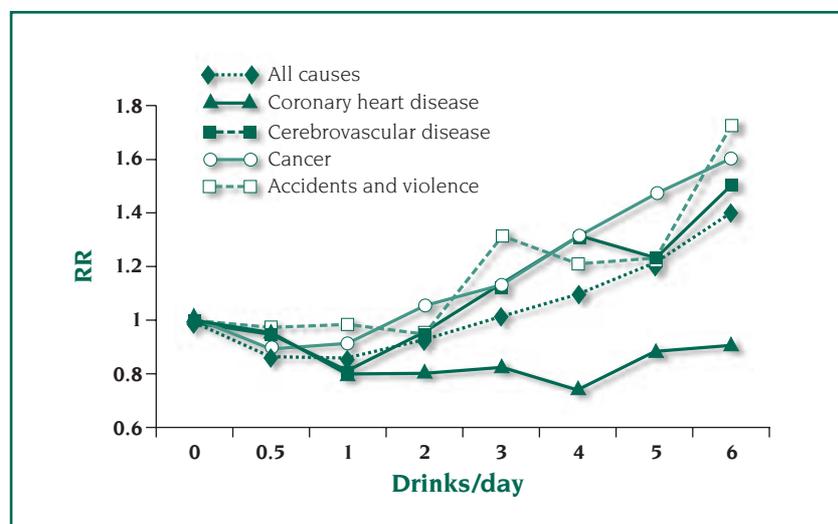


Figure 1. Alcohol drinks per day and relative risks (RR) of all-cause and cause-specific mortality over 12 years in American Cancer Society prospective study of 276 802 men aged 40 to 59 years. RRs adjusted for age and smoking habits.

Modified from reference 8: Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. *Epidemiology*. 1990;1:342-348. Copyright © 1990, Lippincott Williams & Wilkins.

cancer, and accidents and violence, steadily increases, leading to an increase in total mortality, which is after all the bottom line. The large number of subjects and extended length of follow-up make these data particularly useful. Similar findings are found in cross-cultural ecologic studies, where the "French paradox" for wine consumption holds for coronary mortality, but not for total mortality.⁵

Third, the benefit is limited to individuals at increased risk of atherosclerotic cardiovascular disease. By definition, a cardioprotective factor cannot produce a significant benefit unless there is a significant underlying risk. Thus, we would expect little benefit in younger and lower-risk individuals, and in fact the data support no benefit in anyone below the age of 60.^{9,10} In addition, in some studies, benefit is limited to, or particularly noticeable in, subjects with known high baseline risk such as more than one CVD risk factor,¹⁰ diabetes,¹¹ the metabolic syndrome,¹² or elevated LDL chole-

sterol.¹³ While men and women at low risk of atherosclerotic CVD cannot benefit from alcohol consumption, they are nonetheless subject to harm from it. The difference in outcomes between men and women is particularly noteworthy. *Figure 2* shows the results of a pooled analysis of the sex-specific association

between alcohol consumption and total mortality in 14 cohort studies.¹⁴ Note again that a benefit for total mortality is limited to 2 drinks or less per day in men, but that in women the benefit is limited to 1 drink per day or less. This reflects on average greater bioavailability in women for the same dose of ethanol,¹⁵ as well as the known dose-response association between alcohol and breast cancer in women.¹⁶

EXPERIMENTAL STUDIES

In observational studies, alcohol consumption is associated with mostly favorable differences in CVD risk factors.¹⁷ Clinical trials looking at the short-term changes with alcohol on these potential mediators of the alcohol effect by and large confirm these associations to be causal.¹⁸ While most of these changes are favorable (eg, increased high-density lipoprotein [HDL] cholesterol, decreased thrombotic factors), some reverse with alcohol withdrawal,¹⁹ and blood pressure is in fact increased by alcohol consumption.²⁰

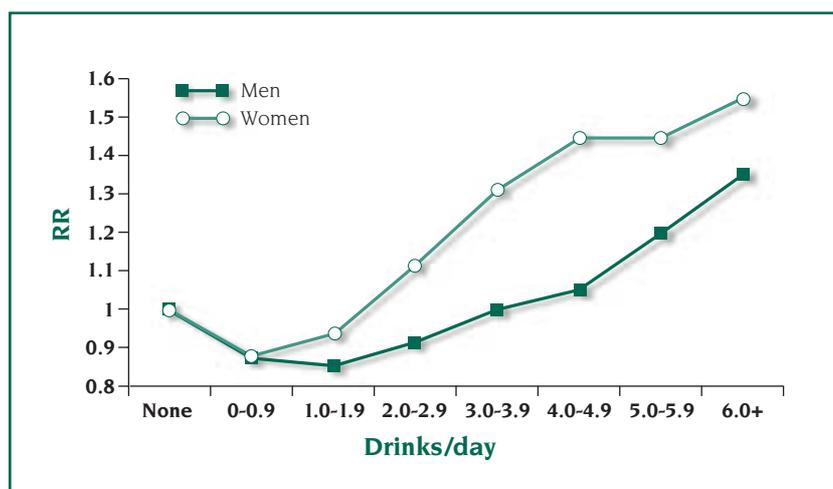


Figure 2. Relationship of usual alcohol intake to all-cause mortality, derived from a pooled analysis of 14 cohort studies. RR, relative risk.

Modified from reference 14: Holman CD, English DR, Milne E, Winter MG. Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations. *Med J Aust*. 1996;164:141-145. Copyright © 1996, The Medical Journal of Australia.

What are the recommendations about alcohol consumption? - Criqui

Although observational data on CVD events and clinical trial data on alcohol's effect on CVD risk factors are informative, particularly when carefully analyzed, we should rely to the extent possible on data from randomized controlled trials on CVD events in making policy recommendations for preventive or therapeutic strategies. In the area of alcohol, this presents a conundrum. There are no randomized trials of alcohol consumption with an end point of CVD events, nor are there likely to be any. Such trials would be difficult to conduct, and of limited value when completed. A true placebo control is not possible, and maintenance of consumption in the experimental (say 2 drinks per day) and in the control (abstinence) groups would be difficult in a randomized study over even a short follow-up, let alone a long one as required in CVD event trials. Thus, in terms of data on CVD events we are limited to inferences from observational data in formulating recommendations. Multivariate analyses of observational data evaluating potential biologic pathways have shown that a beneficial effect of alcohol on CVD events is likely mediated at least in part by increased HDL cholesterol,¹ and a hazardous effect of higher levels of alcohol is mediated by increased blood pressure.²¹ Such observations strengthen the likelihood, but do not guarantee, that alcohol in light-to-moderate amounts is causally protective for atherosclerotic CVD.

However, we should remain cautious since we lack truly definitive evidence. The lesson of hormone replacement therapy in women comes to mind. Just a few short years ago there was general consensus that restoring estrogen in women after the menopause reduced CVD risk, and there was evidence this effect was mediated by the known causal

effect of estrogen in raising HDL cholesterol and lowering low-density lipoprotein (LDL) cholesterol.^{22,23} Despite sophisticated statistical control for potential confounding variables in observational studies, recent clinical trials have proved the consensus was wrong. Not only is there no protection, but estrogen therapy actually increases the risk of atherosclerotic CVD, including coronary disease and ischemic stroke.^{24,25} In addition, recent evidence in younger adults indicates that any level of alcohol consumption is associated with an increase in coronary calcification,²⁶ a potent risk factor for CVD events. The observational findings for light-to-moderate alcohol use seem less likely to be spurious than those for estrogen replacement, primarily because favorable changes in risk factors, such as inflammatory factors, are present more often with light-to-moderate alcohol consumption than with estrogen therapy.^{27,28} although again the beneficial associations for alcohol are limited to light-to-moderate consumption.²⁷ Nonetheless, any recommendations about alcohol consumption should consider the (unlikely) possibility that the observational associations are artifactual.

WHAT IS THE BEST METRIC FOR THE RISK-BENEFIT RATIO?

All of the above studies of CVD events base their conclusions on morbidity and mortality rates in populations. In order to have adequate power, studies typically have an older minimum age requirement. Thus, study participation is predicated on survival to the minimum age for inclusion. CVD events occur disproportionately in older (and higher-risk) adults, and the observed benefit from moderate alcohol consumption is largely at older ages. Let us consider a different metric,

and focus instead on the age range from birth up to the average life expectancy, 75 years. Rather than simply mortality rates, let us use a measure that takes into account the potential years of life lost (PYLL) from a given fatal disease event. In PYLL analyses, a death at age 40 results in 35 PYLL, while a death at age 70 only results in 5 PYLL. Thus, an earlier demise is weighted more heavily than a later one.

Figure 3 shows the data for men for PYLL in 1990 in Canada, and *Figure 4* shows similar data for women.²⁹ Note that in men, while coronary disease is the leading cause of PYLL, motor vehicle crashes and suicide are close behind. Both of the latter outcomes are positively linked to alcohol consumption, and together are associated with about 50% more PYLL than coronary disease. Other alcohol-linked outcomes also make significant contributions to PYLL in men, including HIV infection, stroke, cancer of the large intestine, cirrhosis, and homicide. In women, both breast cancer and motor vehicle crashes contribute more PYLL than coronary disease. Suicide, stroke, cancer of the large intestine, homicide, and cirrhosis also contribute substantially to PYLL in women. Using the PYLL metric as opposed to event rates gives us a better understanding of the overall contribution of alcohol to unfavorable outcomes in populations.

WHAT DO WE RECOMMEND TO INDIVIDUAL PATIENTS?

We can see from the above review that whether the benefits outweigh the risks depends on the patient. Whether the practitioner is a cardiologist, other specialist, or generalist, there is only one group of patients that could potentially benefit from light-to-moderate alcohol con-

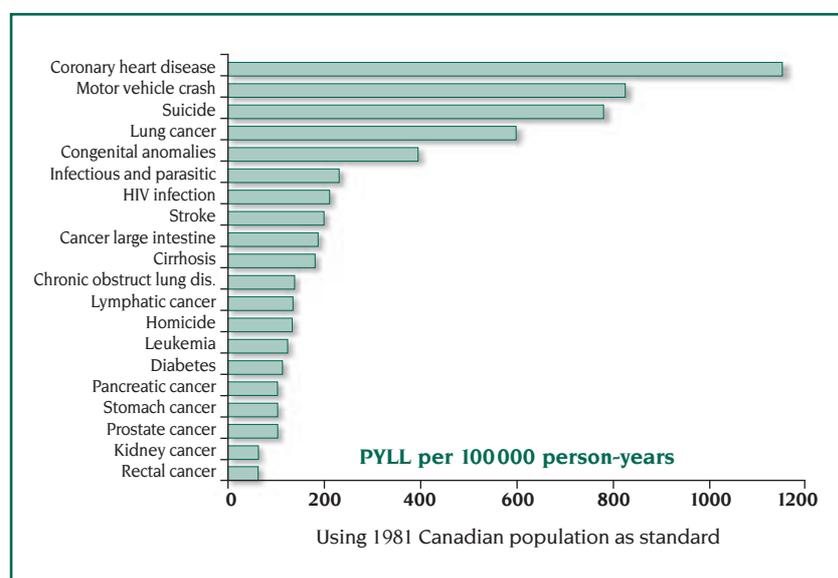


Figure 3. Rates of potential years of life lost (PYLL) before age 75, by cause of death, males, Canada, 1990.

Modified from reference 29: Wilkins K, Mark E. Potential years of life lost, Canada 1990. *Chron Dis Can.* 1992;13:111-115. Copyright © 1992, Minister of Public Works and Government Services Canada.

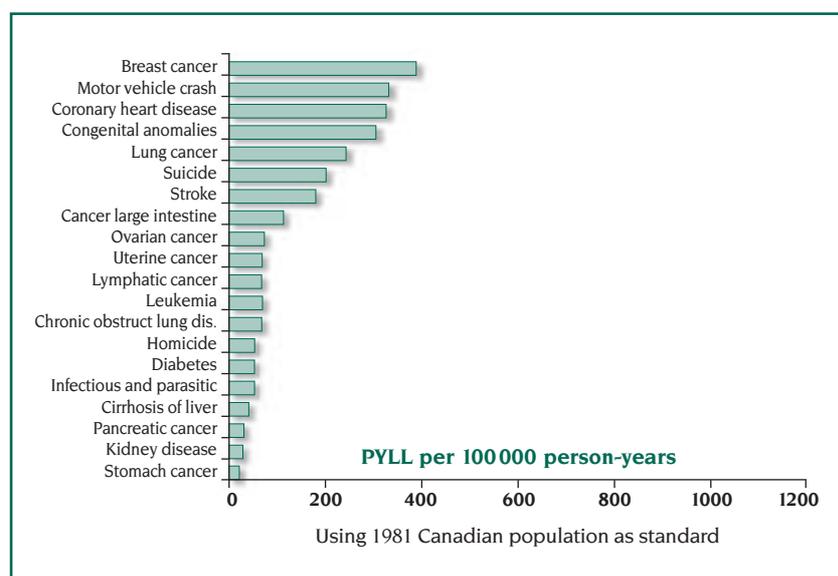


Figure 4. Rates of potential years of life lost (PYLL) before age 75, by cause of death, females, Canada, 1990.

Modified from reference 29: See Figure 3 caption.

sumption, ie, patients at high risk of, or with known, atherosclerotic CVD. But even in this group, recommendations need to be carefully considered. If the patient already consumes alcohol, there is rarely an occasion to suggest increased consumption, since the maximum ben-

efit is obtained at a single drink per day. Should a nondrinker in this high-risk group ever be told to start drinking? Consider the reasons why patients are nondrinkers. Reasons include a personal history of alcoholism; a family history of alcoholism (the risk of alcoholism is four-

fold, and primarily genetic, since concordance in monozygotic twins is twice that of dizygotic); experience with alcohol abuse in relatives or friends; a medical contraindication; a religious, ethical, or moral objection; and dislike of the taste of alcohol or the feeling of intoxication. In which of these abstainer groups would you feel comfortable recommending beginning to drink? Abstaining patients with a history of abuse have been documented to use such a recommendation as an excuse to return to drinking and then alcoholism. Thus, in the clinical setting, the practitioner is ethically essentially limited to discussions encouraging alcohol consumption with nondrinking patients or patients considering quitting drinking who are at high risk of atherosclerotic CVD and known to have neither a personal nor family history of abuse. This is a small target group indeed.

WHAT DO WE RECOMMEND TO THE GENERAL PUBLIC?

In theory, the question here is not really so different from that for the individual patient, ie, there may be benefit for persons at high risk of atherosclerotic CVD and low risk of abuse. However, such messages translate poorly at the population level. The heaviest drinking is done by younger persons,³⁰ who may be susceptible to the suggestion that alcohol is "good for your heart." The alcohol industry advertises extensively in the media, and the ads typically feature young persons partying. The young have nothing to gain and everything to lose by beginning or increasing drinking. Although the alcohol industry has strongly supported "responsible drinking," they also know that since about 8% of the United States adult population are alcoholics, it is mathematically

What are the recommendations about alcohol consumption? - Criqui

inevitable that about half the alcohol production is consumed by alcoholics.³¹ They thus have an economic conflict of interest.

Thus, the most appropriate recommendation to the general public is rather simple—alcohol is a dangerous drug. If this conclusion seems oversimplified, consider what the situation would be if alcohol were a newly discovered pharmacologic agent showing favorable effects on HDL cholesterol and selected other CVD risk factors, and clinical trials were conducted with the aim of a new drug indication for cardioprotection. Clinical trials would report favorable effects on risk factors, but in addition a uniform dose-dependent suppression of coordination and cognitive function, with severe psychosocial dysfunction in some subjects. Given availability, about 8% of subjects in these trials would develop profound addiction with devastating consequences for themselves, their families, and occasionally innocent strangers. Despite the fact that most subjects in these trials would have no problems and would probably receive some cardioprotection, there is no chance a regulatory body such as the United States Food and Drug Administration (FDA) would ever grant approval to a drug with this profile. The risk-benefit ratio would surely disqualify it for licensure. This simple fact should be kept in mind when making any recommendations concerning alcohol consumption.

REFERENCES

1. Criqui MH, Cowan LD, Tyroler HA, et al.

Lipoproteins as mediators for the effects of alcohol consumption and cigarette smoking on cardiovascular mortality. Results from the Lipid Research Clinics Follow-up Study.
Am J Epidemiol. 1987;126:629-637.

2. Reynolds K, Lewis B, Nolen JD, Kinney GL, Sathya B, He J.

Alcohol consumption and risk of stroke: a meta-analysis.
JAMA. 2003;289:579-588.

3. Camargo CA, Stampfer MJ, Glynn RJ, et al.

Prospective study of moderate alcohol consumption and risk of peripheral arterial disease in US male physicians.
Circulation. 1997;95:577-580.

4. Rimm EB, Klatsky A, Grobbee D, Stampfer MJ.

Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine, or spirits?
BMJ. 1996;312:731-736.

5. Criqui MH, Ringel BL.

Does diet or alcohol explain the French paradox?
Lancet. 1994;344:1719-1723.

6. Trevisan M, Schisterman E, Mennotti A, Farchi G, Conti S, and the Risk Factor and Life Expectancy Research Group.

Drinking pattern and mortality: the Italian Risk Factor and Life Expectancy Pooling Project.
Ann Epidemiol. 2001;11:312-319.

7. Criqui MH.

Alcohol and coronary heart disease: consistent relationship and public health implications.
Clin Chim Acta. 1996;246:51-57.

8. Boffetta P, Garfinkel L.

Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study.
Epidemiology. 1990;1:342-348.

9. Klatsky AL, Armstrong MA, Friedman, GD.

Alcohol and mortality.
Ann Intern Med. 1992;117:646-654.

10. Fuchs CS, Stampfer MJ, Colditz GA, et al.

Alcohol consumption and mortality among women.
N Engl J Med. 1995;332:1245-1250.

11. Valmadrid CT, Klein R, Moss SE, Klein BE, Cruickshanks KJ.

Alcohol intake and the risk of coronary heart disease mortality in persons with older-onset diabetes mellitus.
JAMA. 1999;28:239-249.

12. Hein HO, Sorensen H, Suadicani P, Gyntelber F.

Alcohol consumption, Lewis phenotypes, and risk of ischaemic heart disease.
Lancet. 1993;341:392-396.

13. Hein HO, Suadicani P, Gyntelberg F.

Alcohol consumption, serum low density lipoprotein cholesterol concentration, and risk of ischaemic heart disease: six year follow up in the Copenhagen male study.
BMJ. 1996;312:736-741.

14. Holman CD, English DR, Milne E, Winter MG.

Meta-analysis of alcohol and all-cause mortality: a validation of NHMRC recommendations.
Med J Aust. 1996;164:141-145.

15. Thomasson HR.

Gender differences in alcohol metabolism: physiological responses to ethanol. In: Galanter M, ed.

Recent Developments in Alcoholism. New York, NY: Plenum Press; 1995;12:163-179.

16. Longnecker MP, Berlin JA, Orza MJ, Chalmers TC.

A meta-analysis of alcohol consumption in relation to risk of breast cancer.
JAMA. 1988;260:652-656.

17. Criqui MH.

Alcohol consumption and cardiovascular disease. In: Paoletti R, Klatsky AL, Poli A, Zakhari S, eds.

Moderate Alcohol Consumption and Cardiovascular Disease. Dordrecht, Netherlands: Kluwer Academic Publishers; 2000:23-36.



18. Rimm EB, Williams P, Forsher K, Criqui M, Stampfer MJ.

Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors.

BMJ. 1999;319:1523-1528.

19. Haselager EM, Vreeken J.

Rebound thrombocytosis after alcohol abuse: a possible risk factor in pathogenesis of thromboembolic disease.

Lancet. 1977;1:774-775.

20. Criqui MH, Langer RD, Reed DM.

Dietary alcohol, calcium, and potassium: independent and combined effects on blood pressure.

Circulation. 1989;80:609-614.

21. Criqui MH.

Alcohol and hypertension: new insights from population studies.

Eur Heart J. 1987;8(suppl B):19-26.

22. Barrett-Connor E, Slone S, Greendale G, et al.

The Postmenopausal Estrogen/Progestin Interventions Study: primary outcomes in adherent women.

Maturitas. 1997;27:261-274.

23. Bush TL, Cowan LD, Barrett-Connor E, et al.

Estrogen use and all-cause mortality. Preliminary results from the Lipid Research Clinics Program Follow-up Study.

JAMA. 1983;249:903-906.

24. Manson JE, Hsia J, Johnson KC, et al.

Estrogen plus progestin and the risk of coronary heart disease.

N Engl J Med. 2003;349:523-534.

25. Anderson GL, Limacher M, Assaf AR, et al.

Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial.

JAMA. 2004;291:1701-1721.

26. Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB.

Alcohol consumption, binge drinking, and early coronary calcification: findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Am J Epidemiol. 2005;161:423-433.

27. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W.

Effect of alcohol consumption on systemic markers of inflammation.

Lancet. 2001;357:763-767.

28. Cushman M, Legault C, Barrett-Connor E, et al.

Effect of postmenopausal hormones on inflammation-sensitive proteins: the Postmenopausal Estrogen/Progestin Interventions (PEPI) Study.

Circulation. 1999;100:717-722.

29. Wilkins K, Mark E.

Potential years of life lost, Canada 1990.

Chronic Dis Can. 1992;13:111-115.

30. Hilton ME, Clark WB.

Changes in American drinking patterns and problems, 1967-1984. In: Pittman DJ, White HR, eds.

Society, Culture, and Drinking Patterns Reexamined. New Jersey: Rutgers Center of Alcohol Studies: 1991:8.

31. Skog OJ.

The collectivity of drinking cultures: a theory of the distribution of alcohol consumption.

Br J Addict. 1985;80:83-99.



Plants and the Heart

Coca, barley, and the giant reed: the discovery of local anesthetics and their use in cardiology

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About 30 important modern medicines, completely assessed by proper clinical trials, owe their origin in one way or another to plants. Sometimes, as with quinidine, the drug is actually contained within the plant, and on other occasions, as with amiodarone, it was investigation of a plant compound that led to the synthesis of a related, but better drug. So we may ask ourselves the question "How were the plants that yield good medicines discovered in the first place?" Quite often the answer is in folk medicine, long continued trial and error in the community having identified a plant such as the opium poppy as having useful healing properties. But folk medicine is not the only source. Valuable discoveries have been made from veterinary medicine, from large-scale screening programs of plant extracts, from observations by patients themselves, from physicians, and from research in organic chemistry. It is these last avenues of discovery that concern us here, because the local anesthetic action of cocaine was found during a psychiatric study, while lidocaine



Figure 1. Botanical illustration of the coca plant, *Erythroxylon coca* L. Source not identified. All rights reserved.

(lignocaine) was found from a chemical investigation of chlorophyll-defective mutants of barley.

COCAINE

The coca plant, *Erythroxolon coca* L., was sacred to the Incas of Peru, and an account of its properties was published in Seville by Nicholas Mondares in 1565 (Figure 1). Pure cocaine was isolated much later by Albert Niemann

of Gottingen in 1860. It was then used as a mild stimulant, rather like caffeine, and a report that it had helped Bavarian soldiers to counter fatigue led Sigmund Freud to investigate its properties. During one of his experiments, a subject tasted the compound and found that cocaine numbed his tongue, and he mentioned this to one of Freud's assistants, Karl Koller, an ophthalmologist. Koller had been searching for a topical anesthetic for eye surgery, and in 1884 he reported the great value of using cocaine for eye operations. The search then began for a cocaine analog that would be a safe nonirritant injectable local anesthetic, and after many attempts by himself and others, Albert Einhorn of Munich produced procaine in 1910. However, procaine was rapidly metabolized and, finally, in the 1950s, this problem was solved by the introduction of procainamide.¹

The coca plant is a member of the small tropical family *Erythoxylaceae*, which has no other species with medical uses. Coca leaves dried and powdered and mixed with lime are used orally by people in South America to combat fatigue, and allegedly the leaf helps to maintain a good level of blood glucose in spite of a poor diet. Coca-Cola®, introduced in 1886, contained cocaine in the form of coca leaf until 1902. Nowadays cocaine has led

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to a pernicious form of drug addiction with 13 million addicts consuming over 800 metric tons per annum worldwide.

LIDOCAINE

It is probably safe to say that without the purely academic research of a chemist, lidocaine would never have been discovered, especially since it has nothing to do with the development of cocaine analogs. The story starts in 1933 when Professor Hans von Euler of the University of Organic Chemistry in Stockholm (Nobel prize 1929) pioneered a new concept when he sought to identify chemical differences between genetically different types of plant. For his first study, he chose four chlorophyll-deficient mutants of barley, *Hordeum vulgare* L, which he obtained from the famous Swedish plant geneticist H. Nilsson-Ehle (Figure 2). Extracts of two of them showed UV absorption bands typical for indole derivatives, and he isolated the compound responsible for these bands, which he called "gramine" after the name of the plant family *Gramineae*. On elemental analysis it was C11 H14 N2 with a spectrum similar to that of 2-methylindole.² His assistant Holger Erdtman was given the task of synthesizing the compound and having done so he was disappointed that his compound, 2-dimethyl-aminoethylindole, was not gramine. It was in fact an isomer of gramine and was named isogramine. Chemists would often taste a new compound and when he did so Erdtman found that isogramine numbed his tongue, which gramine did not. Using the starting material of his isogramine synthesis, Erdtman and a young chemistry student, Nils



Figure 2. Botanical illustration of barley, *Hordeum vulgare* L. This is not the chlorophyll-deficient mutant.

Reproduced from: Prof Dr Otto Wilhelm Thomé. Flora von Deutschland, Österreich und der Schweiz. 1885, Gera, Germany. With kind permission from Kurt Stüber, Max-Planck Institut für Züchtungsforschung. © 1999.

Löfgren, prepared a number of analogs, which were tested by Ulf von Euler (Nobel prize 1970) with the support of the Astra company.³ But the compounds were too irritant to use as a local anesthetic and it was not until some years later that Löfgren took up the work again. This time, in 1943, he succeeded in producing an excellent compound that differed from one of the original Erdtman and Löfgren

compounds only by the addition of an extra methyl group in the 6 position of the benzene ring (Figure 3). This was Xylocaine, and clinical trials in Stockholm at the Karolinska Sjukhuset led to it being available in 1948 for general use and marketed by Astra. It was entered under that name in the British Pharmacopeia in 1955, but its generic names became lignocaine in the UK and lidocaine in the USA. Gramine had been isolated by Russian chemists in 1935, and called by them donaxine, from the giant or Asiatic reed *Arundo donax* L, which they investigated because it had been noted that grazing camels refused to eat it! (Figure 4) This plant is the "reed" of the Bible and it is used to make clarinet and organ reeds. The plant family *Gramineae* is now called *Poaceae* (all family names for plants now have to end in *aceae*). It is a huge family with 9000 species and of great importance to man, containing rice, maize, wheat, barley, oats, and sugar cane, among others, but none contain therapeutic compounds—indeed, as we have noted, the actual barley compound gramine is inactive medically. Plants in the family range from humble lawn grasses to giant bamboos.

EARLY USE OF PROCAINE IN CARDIOLOGY

While everyone knows about lidocaine in arrhythmias, it is not well known that the use of local anesthetic agents in cardiology goes back a long way. In the early 1930s, Dr Claude S. Beck was undertaking pioneer cardiac surgery at the Lakeside Hospital in Cleveland, Ohio. He was doing pericardial resection for constrict-

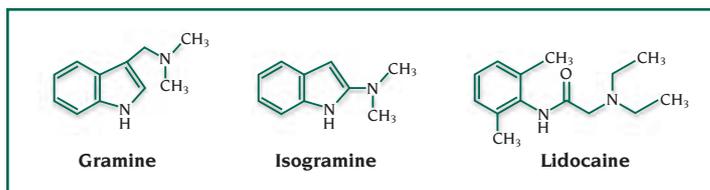


Figure 3. Chemical formulae of gramine, isogramine, and lidocaine (lignocaine, xylocaine).



tive pericarditis, an operation first performed in 1913 by Ferdinand Sauerbruch and reintroduced in 1928, and also attempting to revascularize the heart by suturing a pedicle graft of pectoralis muscle onto the left ventricle. However, arrhythmias during and after surgery, including ventricular fibrillation, presented an important problem, which was investigated experimentally by Dr Frederick R. Mautz. He chose drugs in the cocaine group because they were readily absorbed from mucous membranes and were already known to have some effect on the myocardium. Mautz showed that cocaine produced a monophasic action current in the epicardial electrogram and that it prevented extrasystoles when the heart was stimulated electrically. Beck put procaine hydrochloride into the pericardial sac, with some benefit.⁴

However, the short life of intravenous procaine due to metabolism by esterase enzymes in the blood, plus a high incidence of central side effects, made it a nonstarter for the treatment of arrhythmias. Fortunately, the formulation and introduction in 1951 of procainamide, which was enzyme-resistant and active by mouth, overcame these problems, and the drug became widely used both acutely and chronically for atrial and ventricular arrhythmias. Nevertheless, after it was found that about 80% of patients developed antinuclear factor (ANF) antibodies and 30% got the systemic lupus erythematosus (SLE) syndrome, procainamide had to be withdrawn for the long-term prevention of arrhythmias. Currently, it is hardly used, though it does have one interesting application in that it can unmask the typical electrocardiogram of the Brugada syndrome when this is initially absent.

THE RISE AND FALL OF LIDOCAINE

When Xylocaine, as it was then known, came onto the market in 1948, its main use was as a very effective local anesthetic, especially for dental surgery, but it was not long before its value in cardiology was appreciated with a paper in 1950 by J. L. Southworth et al.



Figure 4. Botanical illustration of the giant, or Asiatic, reed, *Arundo donax* L.

Reproduced from: Prof Dr Otto Wilhelm Thomé. Flora von Deutschland, Österreich und der Schweiz. 1885, Gera, Germany. With kind permission from Kurt Stüber, Max-Planck Institut für Züchtungsforschung. © 1999.

They reported an adult with congenital heart disease in whom ventricular fibrillation (VF) developed during right heart catheterization. Although six electrical countershocks over a period of 40 minutes proved ineffective,

intracardiac lidocaine enabled a seventh shock to restore sinus rhythm.⁵ Lidocaine was soon found to be very effective for ventricular, but not for atrial arrhythmias. The development of coronary care units (CCUs) from 1962 onwards gave a great impetus to the study and management of arrhythmias with acute myocardial infarction (MI), and it was shown by D. G. Julian et al in 1964 that ventricular ectopic beats, especially if they were of the R on T variety often presaged the onset of VF, but that in some cases, especially if the VF developed early, there was no warning.⁶ From an analysis of 600 patients, D. M. Lawrie et al showed that although the risk of VF was greatest in the first few hours after the start of symptoms, when VF developed early in the course of infarction it was seldom preceded by warning arrhythmias.⁷ In 1967, B. Lown et al published a very influential paper based on 130 patients in a CCU, of whom 78% had ventricular arrhythmias. If they were of a certain type, lidocaine was given to suppress them, and no patient developed primary VF. There was no statement as to how soon after the onset of symptoms the treatment was given, nor about the number of patients treated. Lown wrote, "For the first time, it has become materially possible to reduce death resulting from arrhythmias in hospitalized patients with acute myocardial infarction."⁸ This practice was enthusiastically adopted in many hospitals, overlooking the fact that most of the deaths from primary VF occur early without warning arrhythmias. It was true that lidocaine would abolish about 90% of frequent ventricular extrasystoles with acute MI,⁹ and an overview in 1988 from 14 randomized trials showed that prophylactic lidocaine reduced the odds of VF by about one

third.¹⁰ However, it was also the case that this treatment increased the odds of early death by one third: patients given lidocaine were dying from asystole.¹⁰ Carruth and Silverman questioned the use of prophylactic lidocaine. They analyzed 2200 admissions to their CCU (1200 were later documented as having acute MI) and if lidocaine had been given routinely to all, irrespective of arrhythmias, it would have been of no use in the 97% who did not develop VF.¹¹

Prophylactic lidocaine is now no longer used for the prophylaxis of VF in acute MI and the main indication for lidocaine is for its very effective termination of episodes of ventricular tachycardia. It is not recommended for out-of-hospital prophylaxis of ventricular arrhythmias in suspected acute MI.

REFERENCES

- 1. Sneader W.**
Drug Discovery. A History.
Chichester, England: John Wiley and Sons Ltd; 2005.
- 2. von Euler H, Hellström H.**
An indole derivative from two barley strains undergoing chlorophyll mutation.
Z Physiol Chem. 1933;217:23-27.
- 3. Erdtman H, Löfgren N.**
Über eine neue Gruppe von lokalanästhetisch wirksamen Verbindungen [A new group of active local anesthetic relationships].
Svensk Kemisk Tidskrift. 1937;49:163-174.
- 4. Beck CS, Mautz FR.**
The control of the heart beat by the surgeon.
Ann Surg. 1937;106:525-537.
- 5. Southworth JL, McKusick VA, Pierce BC, Rawson FL.**
Ventricular fibrillation precipitated by cardiac catheterization.
JAMA. 1950;143:717-720.
- 6. Julian DG, Valentine PA, Miller GG.**
Disturbance of rate, rhythm and conduction in acute myocardial infarction.
Am J Med. 1964;37:915-927.
- 7. Lawrie DM, Higgins MR, Godman LJ, Oliver MF, Julian DG, Donald K.**
Ventricular fibrillation complicating acute myocardial infarction.
Lancet. 1968;2:523-527.
- 8. Lown B, Fakhro AM, Hood WB, Thorn GW.**
The coronary care unit, new perspectives and directions.
JAMA. 1967;199:188-198.
- 9. Jewitt DE, Kishon Y, Thomas M.**
Lignocaine in the management of arrhythmias after acute myocardial infarction.
Lancet. 1968;1:266-270.
- 10. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S.**
Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized controlled trials.
JAMA. 1988;260:1910-1916.
- 11. Carruth JE, Silverman ME.**
Ventricular fibrillation complicating acute myocardial infarction. Reasons against the routine use of lidocaine.
Am Heart J. 1982;104:545-549.

The influence of dietary fats on serum lipid levels in man

E. H. Ahrens, J. Hirsch, W. Insull, T. T. Tsaltas, R. Bloomstrand, M. L. Peterson

Lancet. 1957;1:943-953

One of the most striking aspects of this seminal paper is the quality of the research presented, and the profound questions that are raised about the fundamental influence of the quantity and quality of dietary fats upon the serum lipid profile. Therefore, this work provided the cornerstone for many of the investigations, which will be described later. A second remarkable feature is the fact that experiments were performed with human as opposed to animal subjects, and their rigorous basic design is replicated in much of the later work in this field.

The authors summarize a number of different studies to clarify the influences of dietary fat. Fundamental to all is the principle of each study subject consuming a liquid diet with varying proportions of protein (15%), fat (40%), and carbohydrate (45%), while maintaining a constant calorific intake and body weight throughout the study period, which varied from 4 to 6 months. By feeding the subjects on corn oil in the first part of their dietary regimen, a steady state of serum cholesterol level was achieved for any given individual, and was therefore used as a baseline for comparison.

The first of these studies describes an investigation into why a diet of corn oil might be responsible for the observed reduction in total serum cholesterol. The first question asked is whether the fall is due to the absence of elevating factors or to the presence of lowering factors, but previous work by their group had established that the addition of extra-dietary cholesterol would not lead to a rise in serum cholesterol. Therefore, the next issue was to determine which constituent of the corn oil was the cholesterol-lowering factor. Studies manipulating the proportion of the nonsaponifiable, ie, nonglyceride fraction of corn oil without significant changes in the cholesterol-lowering effect led to the suggestion that the glycerides themselves were the cholesterol-lowering factors.

The next part of the investigation therefore focused on the components of the fatty acid fraction. The authors found that by varying the proportion of fats with a higher iodine value, ie, those with more double bonds (unsaturated fats),

the lipid levels would show a good correlation, such that higher iodine values corresponded with lower cholesterol levels. However, what was less clear was whether the lipid-lowering effect was due to unsaturated fats in general or to a specific variety of unsaturated fat, because the study oils used were so heterogeneous, and pure fatty acid synthesis was prohibitively expensive. Pursuing a similar line of enquiry, however, using partially hydrogenated corn oil to produce a greater proportion of saturated fat, did not lead to firm conclusions in the 3 patients that were studied, although there was a tendency for the saturated fat diet to lead to higher serum cholesterol.

The next stage of investigation was based on the finding that the higher cholesterol levels were observed in the saturated fat-fed groups, but these fats also happened to have short to intermediate carbon chain lengths. Therefore, 2 subjects were fed butter and cocoa butter, containing short- and intermediate-length chains, respectively, but each having near-identical iodine values. The results suggested that the shorter carbon length properties of the butter diet led to higher serum cholesterol.

The authors concluded after these fascinating experiments that modification of food habits, even for those most at threat from atherosclerosis, was not recommended until a more complete understanding of dietary fat and serum cholesterol was obtained, as many aspects remained unexplained. However, the contribution of this study to focusing the direction of future investigations is unmistakable.

1957

The Pulitzer biography prize is awarded to John F. Kennedy for his book "Profiles in Courage"; Great Britain performs atmospheric nuclear tests at Christmas Island; and Joseph R. McCarthy, the driving force behind the anticommunist crusade in the US, dies



Prediction of serum cholesterol responses of man to changes in fats in the diet

A. Keys, J. T. Anderson, F. Grande

Lancet. 1957;2:959-966

This paper is remarkable for several reasons. Firstly, it sets out to achieve what at first sight appears to be a near-impossible task, that is, to demonstrate a method for predicting serum cholesterol changes from the dietary source.

Secondly, where previous and subsequent studies had sought to compare formula (usually liquid) diets with each other, this study attempts to measure the effects of test fatty acids within so-called "ordinary" diets. Astonishingly, the test subjects include exclusively schizophrenic patients in the American arm of the study (whose consent to participate was obtained from their "nearest relative"), as well as coalminers of Japanese nationality in the second arm, bearing in mind that the Second World War had finished a little over 10 years previously. Finally, having expended considerable time and resources in the execution of the study, much of the discussion centers upon reasons why the "predictive" model serves very limited use outside the strict experimental parameters! The authors argue that lowering any type of fat ingested, whether animal or vegetable, may have significance.

Groups of between 12 and 27 men were given calorie-balanced diets, which were controlled so that each was maintained for 4 weeks on "normal" diets (composition not specified). They were subsequently fed for between 2 to 9 weeks on each of 2 to 6 diets that differed in their fat content (between 9% and 44% of total calorie value of the diet), with the experimental fats comprising approximately 75% of the total fat content. The study fats included butterfat, hydrogenated coconut oil, olive oil, cottonseed oil, corn oil, sunflower seed oil, safflower oil, sardine oil, and the mixed food fats of an "ordinary" American diet.

The authors are careful to indicate that an analytical method of predicting the cholesterol response will depend crucially upon the reliability of the assay used to measure cholesterol, and they provide a measure of the error by repeating the assay on duplicate samples for each blood test.

The results that follow are portrayed in a way that is less focused upon identifying components of a fat diet that

may alter serum cholesterol, than they are in providing the means to construct equations that describe the relative influences of saturated, monoethenoid and polyethenoid fats upon serum cholesterol. Consequently, there is relatively little emphasis on the finding that saturated fatty acids (S) with carbon chains longer than 10 have nearly twice as much potential to raise serum cholesterol as the cholesterol-lowering effect of an equal mass of polyethenoid fats (P), and monoethenoids (M) are deemed to exert an almost neutral effect. Instead, there is a complicated, and occasionally baffling analytical process that results in a series of regression equations that describe a surprisingly linear relationship between the fatty acid variables mentioned expressed as calorific values and changes in serum cholesterol:

$$\Delta\text{Cholesterol} = 2.76\Delta S + 0.05\Delta M - 1.35\Delta P - 1.68.$$

However, with the intention of simplifying further the analysis of any particular diet to determine its effect upon serum cholesterol, a mathematical relationship is constructed using the total iodine value as a measure of the average saturated fat content of a diet, although the predictive value of the resulting regression equation is less than that achieved with the previous model when any individual participant's data is subjected to the equations; rather, these equations are better at predicting values for a group than an individual.

Although ultimately flawed, this study provided a benchmark for future attempts to create a regression model for predicting changes in serum cholesterol.

1957

The USSR launches Sputnik 2,
containing Laika, the dog;
the remains of Captain Bligh's ship
"The Bounty" are found off Pitcairn Island; and
Diego Rivera, the Mexican mural painter, dies

Quantitative effects of dietary fat on serum cholesterol in man

D. M. Hegsted, R. B. McGandy, M. L. Myers, E. J. Stare

Am J Clin Nutr. 1965;17:281-295

Both similarities and striking differences are to be found between this paper and previous studies seeking to discover a mathematical prediction of the effect of dietary lipids upon serum cholesterol. It is remarkable considering the nature of the patient cohort and the duration of the study. The participants consisted of 2 groups of 10 mostly schizophrenic men all selected from a psychiatric institution, who were furnished with experimental diets over a period of 2 years. They were fed a relatively low-fat diet (after a control period of 4 weeks eating a "usual" American diet) to which a wide variety of test fats of equal calorific value were added so that total dietary fat was 22% or 38% to 40% of total calorie intake, each test period lasting 4 weeks, and alternated with control diets of varying intervals. Dietary cholesterol was also varied by the addition of egg yolk. Despite the relatively small numbers, by using the same individuals throughout the study period, the authors infer that the conclusions drawn should be "strong."

They begin by describing the key findings of work published to date, including the correlation between the degree of saturation (iodine number) of a fat and serum cholesterol, the multiple regression equation of Keys linking serum cholesterol changes with calorific values of mainly saturated and polyunsaturated fats, the conflicting evidence for polyunsaturated fats and dietary cholesterol, and the relative lack of data for dietary phytosterols, carbohydrates, and proteins.

By collating the data and submitting them to an IBM machine (presumably the grandfather of modern computers), the investigators obtained 256 equations that represented, with varying degrees of accuracy, a model for predicting serum total cholesterol using each of 8 dietary variables (5 different saturated fatty acids, monounsaturated, polyunsaturated fatty acids, and dietary cholesterol.) As in previous studies, changes in the β -lipoprotein fraction paralleled changes in total cholesterol, although in contrast to earlier studies, the pretest cholesterol levels of individuals did not influence their response to the test diets.

A multiple regression equation was obtained which was adequate to explain 91% of total cholesterol changes, but using only the variables of myristic acid (14 carbon atoms, no double bonds, ie, a saturated fat; [14:0]), palmitic acid (16:0), polyunsaturated fats and dietary cholesterol; inclusion of other variables did not significantly alter the correlation. The most important of the fatty acid components affecting serum cholesterol was the saturated fat myristic acid, whereas palmitic (16:0) and stearic acids (18:0) did not exert a significant effect. Dietary cholesterol unsurprisingly showed a linear relationship with serum cholesterol, in line with most of the current studies, although this finding was at odds with one previous work. As previously shown, increasing the polyunsaturated portion lowered serum cholesterol. Interestingly, the amount of fat consumed, whether 22% or 40% of total intake, had no influence on serum cholesterol, but a more accurate prediction could be made from considering the proportions of different dietary fatty acids. The authors summarize by suggesting that practical means of lowering cholesterol by diet is to include fats with a relatively small proportion of myristic and palmitic acids and cholesterol, and a high proportion of polyunsaturated acids.

The authors conclude with a honest appraisal of the limitations of multiple regression equations, namely, that they are simply descriptions of the results obtained, and that the dietary oils act as though their specific fatty acids have the influence upon serum cholesterol proportional to their coefficient. However, they do not prove per se that the fatty acids have these effects.

1965

Folk rock is born when Bob Dylan is booed off stage at the Newport Folk Festival for using electric instruments; France's president De Gaulle and the Italian president Saragat officially open the Mount Blanc tunnel; and death of Japanese writer Junichiro Tanizaki



Serum cholesterol response to changes in the diet. IV. Particular saturated fatty acids in the diet

A. Keys, J. T. Anderson, F. Grande

Metabolism. 1965;14:776-787

Amidst the abundance of regression analyses and equation-solving that characterizes both this paper and the previous one from this group that is discussed in these summaries, there does appear to be at least one clear conclusion: dietary stearic acid does not have a serum cholesterol-raising effect. This conclusion is reached, however, not from a specific investigation into the effects of dietary stearic acid per se, but by an attempt to understand why the chosen formula relating serum cholesterol changes to dietary intake of fatty acids does not appear to provide a reliable estimate in many instances. This formula is:

$$\Delta \text{Cholesterol} = 1.35 (2\Delta S - \Delta P) + 1.5\Delta Z,$$

where S and P are the percentage of total calories provided by saturated and polyunsaturated fats, respectively, and $Z^2 = \text{mg of dietary cholesterol per 1000 calories}$.

Previous work by this group led to a derivation of this formula from a rather specific patient population with specific test diets, as described above. The implication of the formula is that all saturated fats exert an equal effect upon dietary cholesterol, whereas the coefficient value of S was derived from mixtures of saturated fats, with possible different dietary effects. Even by exclusion of small carbon chain length fatty acids, which the authors argue have different physical properties and therefore different metabolic fates compared with their longer-chain length counterparts, the effect upon the discrepancies noted by using the formula to estimate serum cholesterol changes is negligible, presumably because such small-length chains do not occur in any normal diet.

Attention is then turned to experiments with cocoa butter, where the largest differences are seen between observed and expected results using the formula for any particular diet. The authors indicate that one distinguishing characteristic of this food is its high stearic acid content. Based on this observation, they suggest that there may be three explanations why stearic acid analysis leads to higher than expected errors, which are: (i) stearic acid has a neutral effect upon cholesterol and should be subtracted from the

“S” value prior to calculation; (ii) stearic acid actually has a cholesterol-lowering effect; and (iii) stearic acid interferes with the cholesterol level-modifying properties of other fats. The authors then proceed to reanalyze 46 different lines of evidence from several different studies in order to explore these concepts further.

The remainder of the paper appears to be an exercise in justifying the validity of the original regression equation, albeit with sufficient modification to take into account the various stearic acid diets analyzed. The equations that lead to the most accurate prediction of serum cholesterol levels are those that exclude stearic acid from the calculation.

The authors conclude that stearic acid is not cholesterol-elevating and that, therefore, the other constituents of saturated fat, chiefly lauric, palmitic, and myristic acids, have the greatest influence upon raising cholesterol levels.

This paper once again demonstrates the shortfalls in ascribing too great an importance to regression analyses; each equation is ultimately a description of observed data, but if the data itself are limited, or if assumptions are made about the constituent parts of the data that cannot be validated reliably, then the predictions will be inaccurate.

1965

Rhodesian Prime Minister Ian D. Smith
unilaterally proclaims independence from Britain;
Ferdinand Marcos claims victory in the Philippines
presidential election; and Joseph Mobutu
deposes Congo President Joseph Kasavubu
and installs himself as the head of state

The Seven Countries Study: 2289 deaths in 15 years

A. Keys, A. Menotti, C. Aravanis, H. Blackburn, B. S. Djordjevic, R. Buzina, A. S. Dontas, F. Fidanza, M. J. Karvonen, N. Kimura, et al

Prev Med. 1984;13:141-154

Epidemiological studies such as this rely on a long duration of follow-up (in this case 15 years) to obtain significant results, a period made all the more poignant in this case by the fact that two of the authors died before it reached publication. The primary goal was to investigate the causes of death in men apparently free of cardiovascular disease from the initiation of the study, and potentially use the data to predict and prevent deaths across various different populations.

There were 15 cohorts from 7 countries, grouped further into 4 regions (USA, Northern Europe, Southern Europe, and Japan). Several risk factors were examined to assess their contribution for both coronary and all-cause mortality; these were age at entry, serum cholesterol, systolic blood pressure, smoking, body mass index (BMI, termed “relative body weight”), and physical activity.

Several problems become immediately apparent with the study methods and design. Firstly, despite a study population of just over 11 500, no women were included. Secondly, the range of ages investigated is relatively narrow (40 to 59 years). Thirdly, information about arguably the most important data, the cause of death, was obtained variously from death certificates, insurance companies, and from friends and relatives of the deceased. The authors themselves point out the limitations of such methods, particularly in areas such as rural Japan where coronary artery disease-related death was a relatively new diagnosis, and could potentially be missed. Despite stipulating the intention to document causes of premature death, no mention is made of how this might be defined. Crucially, information is lacking about the method of describing how an individual was deemed to be free of cardiovascular disease before allowing entry into the study. Finally, the statistical method used to calculate the probability of death for the various risk factors was a multiple logistic model derived by an iterative method described nearly 20 years earlier, without any apparent validation.

So despite these limitations, several conclusions were drawn from the results. Of the 11 579 men deemed to be

free from cardiovascular disease, 2289 died in 15 years, 618 of coronary disease. Systolic blood pressure appeared to be the only factor on entry to the study that explained differences in all-cause mortality, although the values of blood pressure are not specified. For variances among regions in coronary death, serum cholesterol and blood pressure had the most influence. As might be expected, the coronary mortality risk for individuals was significantly affected by age, serum cholesterol, blood pressure, and smoking (number per day unspecified), although somewhat surprisingly, BMI did not affect risk. Japan was the exception, where too few individuals died of coronary disease to make an evaluation. Physical activity only had an influence in Southern Europe. Similarly, for all-cause death, age, blood pressure, and smoking were significant, except in Japan, and BMI was now a negative risk factor, that is, the probability of death from all causes decreased with increasing BMI.

The investigators then used their findings to compare risk factors for coronary death among regions, and found that trends in mortality for the USA and northern Europe were closely correlated, but could be used to predict trends in Southern Europe, and vice versa. This final point, that different populations may have an intrinsic difference in their response to coronary risk factors, is perhaps the most important conclusion, but due to the various critical flaws of study design and methodology it is not clear if this, and other conclusions, are valid.

1984

Ingmar Bergman’s classic film “Fanny and Alexander” wins the best foreign film award at the Oscars; British ice dancing team, Torvill and Dean, become the first skaters to receive 9 perfect 6.0s in world championships; and South-Africa and Mozambique sign a pact banning support for each other’s internal foes



Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man

F. H. Mattson, S. M. Grundy

J Lipid Res. 1985;26:194-202

This study was published at a time when questions were being raised about the long-term safety of polyunsaturated fats, and as a result carbohydrates were being recommended as a replacement for saturated fatty acids in the diet. There were, however, even fewer data about monounsaturated fats, whose effect upon plasma lipids was thought to be neutral. This paper aimed to compare the effects of saturated, monounsaturated, and polyunsaturated fats upon the serum lipid profile, represented by palm oil, high oleic safflower oil, and high linoleic safflower oil, respectively. A small number of individuals (n=20) were given a rather daunting liquid diet of which 40% total calorific value was given by these fats, which represented the only fats in the diet. The relative proportions of carbohydrate and protein were 44% and 16%, respectively. Each diet was consumed for 4 weeks before switching to the next diet, and the order of the diets was randomized. All but two had elevated plasma total cholesterol at the beginning of the study, defined as greater than 200 mg/dL. Twelve had normal triglyceride levels, while the remaining 8 had elevated levels. These two groups were analyzed separately because of a presumed disturbance of lipid metabolism in hypertriglyceridemic individuals.

In the group as a whole, both monounsaturates and polyunsaturates produced almost identical reductions in low-density lipoprotein (LDL) cholesterol levels (17%) compared with saturates, but no changes in high-density lipoprotein (HDL) levels were observed. Similar reductions in total cholesterol were also observed in these groups compared with saturates, which was different from previous studies that had demonstrated a more marked reduction with polyunsaturates compared with monounsaturates. When normotriglyceridemic patients were considered separately, a significant reduction in HDL cholesterol was seen in the polyunsaturated group. Within the groups, however, there was marked variability in HDL cholesterol response, and the authors emphasize that the small patient numbers prevent firm conclusions from being drawn. Additionally, there was no significant reduction in total cholesterol level with polyunsaturates and monounsaturates. Once again,

these results were in conflict from the earlier studies by Keys, who had produced a model for predicting the change in total cholesterol for a given increase in saturated fats (an increase in total cholesterol), as well as for a given increase in polyunsaturated fats (leading to a decrease in total cholesterol). These results, therefore, suggested that the earlier models were incomplete, and also that a non-linear response in serum lipids to changes in dietary fats might exist.

When the 8 patients with hypertriglyceridemia were considered, a significant reduction in total cholesterol was observed in the polyunsaturate group, but not in the monounsaturate group. By contrast, the monounsaturate group, but not the polyunsaturate group, produced a fall in LDL cholesterol. None of the three fat varieties changed the level of HDL cholesterol in the hypertriglyceridemic group, although levels of HDL cholesterol were generally lower.

Therefore, the general conclusion from the paper was that monounsaturated fats have at least as important a role as polyunsaturated fats in reducing LDL cholesterol levels and total cholesterol, whereas a reduction in HDL cholesterol was seen in normotriglyceridemic patients taking polyunsaturates.

1985

Madonna's "Like a Virgin" album reaches number one in the USA and music charts worldwide; Desmond Tutu is enthroned as the first black Anglican Archbishop of Johannesburg; and Isobel Peron resigns as the head of the Peronist party in Argentina

Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol

S. M. Grundy

N Engl J Med. 1986;214:745-748

Unlike previous studies focusing upon the comparison between polyunsaturated and saturated fats, this is one of the first studies to compare the impact upon plasma lipids of diets rich in carbohydrate (consequently low in fat) with those rich in monounsaturated fats. This study investigated the relative influences of carbohydrates and monounsaturated fats upon the plasma lipid profile, in the context of the relatively low rates of atherosclerotic disease observed in epidemiological studies of Mediterranean diets, despite their relatively high intake of fats in the form of monounsaturated olive oil. Additionally, the study also provides a means of considering the established benefits of a low-fat diet (low rates of coronary heart disease, holding body weight down), against its potential disadvantages.

Remarkably small numbers of trial participants were involved (n=11), and with a ratio of 10 men to 1 woman, this study is thrown into stark relief by modern trials in which patient numbers run into several thousands with equal sex distribution before they are taken seriously. These brave individuals were selected to take part in the trial, which involved consumption of three different liquid diets of equal energy content, each over 4 weeks, selected in a random order for each individual. In two of the diets, 40% of the total energy came from fats and 43% from carbohydrate, and in the third diet just 20% was from fat, but 63% from carbohydrate (the so-called low-fat diet.) In the two fat-rich diets, the principal fat components differed between saturated and monounsaturated fats, respectively. The study was subdivided further into two further categories based upon whether the saturated fatty acids were composed of short chains (mainly coconut oils), or long chains (palmitic acid), but as there were no obvious differences in response compared with the monounsaturated group and the carbohydrate group, the saturated fats were considered as a whole for data comparison.

Interestingly, the monounsaturated diet and low-fat diets both lowered total cholesterol and low-density lipoprotein (LDL) significantly. In addition, the high monounsaturated

fat group had a significantly lower level of total cholesterol compared with the LDL group. Unsurprisingly, the plasma triglycerides were raised with the low-fat, carbohydrate-rich diet, as had been demonstrated by earlier groups, although the authors argue that the observed fall in triglyceride levels seen in individuals who have a prolonged carbohydrate-rich exposure from previous studies was not seen possibly because the 4-week test diet period was too short. However, the low-fat diet also reduced the level of high-density lipoprotein (HDL) cholesterol compared with the other two diets, which had very little effect upon this factor. As a consequence, the LDL/HDL ratio was significantly higher in the low-fat group compared with the monounsaturated fat group.

The authors conclude that a high monounsaturated fat diet can lower the LDL and total cholesterol, together with a neutral effect on HDL. At the same time, however, this diet would have similar or more positive effects upon the plasma lipid profile as a high carbohydrate diet, as long as body weight does not change.

1986

Richard Manuel, rock vocalist and pianist with the "Band," commits suicide at the age of 40 years; Jacques Chirac becomes Prime Minister of the French government; and "Out of Africa" wins best film at the 58th Academy Awards



Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels

A. Bonamone, S. M. Grundy

N Engl J Med. 1988;318:1244-1248

An important question regarding the relative effects of different saturated fats upon the serum lipid profile is addressed in this study: do all saturated fats have a deleterious influence? Two important reasons why this question needs to be asked at all is that saturated fats are present in many animal fats, present in most Western diets, and, secondly, they provide texture in many foods. This experiment could only have been performed without prohibitive costs in a more modern era where relatively inexpensive synthesis of specific fatty acids was made possible, which may explain why this issue was not conclusively dealt with before.

The key piece of evidence suggesting a nonelevating effect of stearic acid (18 carbon atoms, no double bonds [18:0]), found in a high proportion in fats, such as beef, upon cholesterol came from Ahrens in 1957, who observed this phenomenon in the naturally occurring stearic acid-rich cocoa butter. As other evidence has suggested a cholesterol-elevating effect of palmitic acid (16:0), and a lowering effect of oleic acid (18:1), these two fats were used as a comparison with stearic acid in 11 male inpatients of a metabolic ward. Each subject was given three different diets, respectively containing the three different oils, with the order of the diets randomized. Each test diet period lasted for 3 weeks, with a washout period between diets. As in previous studies, the relative proportions of calorific value were fixed among diets, such that 40% came from fats, 40% from carbohydrates, and 20% from milk protein, with a small, fixed cholesterol content of less than 100 mg. The authors are clear in pointing out that the study fats in each diet were not the only fats present, such that the stearic acid-rich diet also contained small amounts of palmitic acid, and the oleic and palmitic acid-rich diets each contained a small portion of stearic acid.

The results showed that the stearic acid diet not only significantly lowered plasma cholesterol, low-density lipoprotein (LDL), and the LDL/HDL (high-density lipoprotein) ratio, but also produced this effect with as much potency as the oleic acid-rich diet, with a tendency for being even

more effective, although this latter finding was not statistically significant. Triglycerides and HDL levels were unchanged with the oleic acid-rich diet when compared with the other two diets. As expected, the palmitic acid-rich diet led to higher total and LDL cholesterol compared with the other two groups.

The investigators also measured the fatty acid composition of plasma triglycerides and cholesterol esters, and discovered that both the oleic acid-rich and the stearic acid-rich diet intriguingly led to a rise in oleic acid in plasma compared with the palmitic acid-rich diet, and yet the stearic acid level in plasma remained unchanged. Some suggestions are made as to why cholesterol is not elevated in the stearic acid-rich diets. One is that this fatty acid may be less well absorbed, but this is unlikely as the subjects did not lose weight while on this diet, and animal studies have suggested otherwise. Secondly, they hypothesize that stearic acid is rapidly converted into oleic acid.

The investigators conclude by pointing out the major flaws in this study, principally that men, but not women, were enrolled, and, secondly, that the effects observed in artificially created dietary fats should not be extrapolated to include naturally occurring foods. Thus, the investigation provides a useful insight both into underlying metabolic fates of certain fats, and also into potential methods of modifying manufactured foods to lessen the impact upon serum lipids.

1988

Chet Baker, the jazz trumpeter,
falls to his death from a hotel window, aged 59;
the Edgar Degas statue "Danseresje van Veertien"
sells for \$10 120 000 at auction; and
Soviets begin their phased withdrawal
from Afghanistan

Effects of dietary *trans* fatty acids in high-density and low-density lipoprotein cholesterol levels in healthy subjects

R. P. Mensik, M. B. Katan

N Engl J Med. 1990;323:439-445

Prior to the publication of this paper, there were reports that drew conflicting conclusions about the influences of dietary fatty acids upon serum lipids. This study was designed to investigate the influence of different varieties of fatty acid components of a diet. Particular attention is given to the distinction between *cis* and *trans* isomers of oleic acid. Both contain one double bond, and are by definition monounsaturated, but because the *cis* isomer has carbon chains that are oriented in the same direction around the double bond, crystallization of the molecules is less likely than with the *trans* isomer whose chains are pointing in opposite directions. The differences between the isomers extend beyond mere molecular geometry, however. Most naturally occurring fats and oils contain *cis* isomers, with the exception being milk fats, which are predominantly *trans* isomers. Synthetic oils, by contrast, which are produced by hydrogenation of unsaturated compounds such as margarines, adopt a *trans* configuration. Particular interest is drawn to the distinction between isomers because the investigators quote an average daily *trans* fatty acid intake as being 6% to 8% of total fat intake in the US diet. They argue that the pressure to decrease the intake of saturated fat in the diet based on previous studies leads to a greater consumption of *trans* fatty acids, as they are the most suitable alternative for the food industry for producing semisolid and solid fats.

The study investigators recruited 59 students who were willing to enter a trial in which they would follow three diets for 3 weeks each, with no washout period between diets. One diet was high in oleic acid (a monounsaturated acid with the *cis* configuration), the second one high in *trans* isomers of oleic acid, and the third high in saturated fats. Interestingly, the experimental design allowed just 10% of the overall energy intake of the diets to be controlled in terms of the fat composition. The remainder of the energy intake was similar across diets for total calorific value, as well as proportions of carbohydrate, protein, fiber, alcohol, and cholesterol. The participants were categorized in 6 groups according to sex, and use of oral contraceptives (for women), so that each group had near-identical num-

bers in each category. Then each group followed the three diets in different orders, working on the investigators' assumption that serum lipoprotein levels stabilize within 2 weeks after a dietary change.

The results would lead to a striking conclusion—that all classes of fatty acids that are substituted for carbohydrates in the diet do not necessarily increase high-density lipoprotein (HDL) cholesterol levels. Indeed, *trans* isomers in this study actually produced a reduction in HDL cholesterol levels to a degree greater than carbohydrates alone would have produced. Additionally, due to an increase in low-density lipoprotein (LDL) cholesterol levels with *trans* isomers (an effect also seen with the saturated fats diet, but to a greater degree), the LDL/HDL ratio increase was more pronounced in the *trans* isomer group compared with the saturated fats group. Both the *trans* fatty acid and saturated fat diets led to an increase in serum triglyceride levels.

What was not clear, however, was whether the relationship between intake of *trans* fatty acids and serum lipid levels was linear. Additionally, the authors were keen to emphasize that the results should not be extrapolated to fatty acids containing a higher number of carbon atoms than oleic acid, or even to *trans* fatty acids of any variety other than oleic acid. However, given the emerging evidence, they recommended that patients with atherosclerosis should reduce their intake of *trans* fatty acids.

1990

Blues guitarist Stevie Ray Vaughan dies
in a helicopter crash aged 35;
Iraqi forces invade Kuwait ; and
Benazir Bhutto is fired as prime minister of
Pakistan and her government dissolved



Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein

D. J. Jenkins, C. W. Kendall, A. Marchie, D. A. Faulkner, J. M. Wong, R. de Souza, A. Eman, T. L. Parker, E. Vigden, K. G. Lapsley, et al

JAMA. 2003;290:502-510

Jenkins et al investigate the intriguing hypothesis that dietary modification may have comparable benefits to a first generation statin (lovastatin) in altering low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and C-reactive protein (CRP) levels. The study is framed in the context of the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program (NCEP), recommending diets low in saturated fats and high in plant sterols and viscous fibers, and the American Heart Association (AHA) drawing attention to potential benefits of soy proteins and nuts. The authors indicate that previous studies examining the reduction in cholesterol by dietary manipulation had resulted in a relatively small reduction in cholesterol compared with statin use. However, there were no studies to date examining the impact of a more robust attack upon dietary fat intake incorporating the food items mentioned above.

Forty-six hyperlipidemic individuals with a mean body mass index (BMI) of 27.6 (range 20.5 to 30.5) were recruited and randomized to one of three vegetarian diets: a control group with a low-saturated fat and high-fiber content including skimmed milk, fat-free cheese; another group with the same low-saturated fat content, but with the addition of lovastatin 20 mg; and a third group taking the so-called combination dietary portfolio, incorporating viscous fibers, soy protein, plant sterols, and almonds. The nonlovastatin groups were given placebo controls. Prior to starting on this diet, there was a 4 week "run-in" period in which each participant followed their own low-fat diet, and any that were taking statins prior to the study diet were asked to stop at least 2 weeks beforehand. The study participants then started on their diets with a 7-day rotating menu plan, while their compliance was monitored using weekly checklists and return of uneaten foods. The use of the statin was double blinded, although the diet regimen was not blinded to the dietitians who were responsible for the patient diets and checking dietary records.

Compliance was surprisingly good in all 3 groups (93% for control, 95% for statin, and 94% for dietary portfolio), al-

though one must bear in mind that the participants were potentially more motivated to comply than a randomly selected group. The results indicated that although the control group managed a small, but significant, reduction in LDL cholesterol compared with baseline (2.1%, $P=0.002$), there was no difference in the LDL/HDL ratio, or in CRP levels. However, in both the statin and dietary portfolio group, there was a greater reduction in LDL cholesterol levels (3.6% and 3.2%, respectively), LDL/HDL ratio (4.2% and 3.2%), and in CRP levels (8.3% and 10.8%). Moreover, there was no significant difference in the level of improvement between the statin-treated and dietary portfolio-treated groups.

The authors suggest that there is an additive effect of the components of the dietary portfolio because of their different modes of action resulting in marked benefits vs the control group. Bile acid excretion is promoted by viscous fibers, cholesterol absorption is reduced by plant sterols, soy proteins reduce hepatic synthesis of cholesterol and increase LDL receptor levels, and almonds contain plant sterols and monounsaturated fatty acids that reduce LDL cholesterol levels. This was also the first study to demonstrate a reduction in CRP levels by dietary modification.

This study offers an alternative lipid-lowering technique to individuals intolerant of statins, or those who are reluctant to take them, although strong motivation and a penchant for nuts and soy beans is recommended!

2003

A fireworks factory in China explodes, killing 29 people; "Kuno the Killer," a giant 5-ft, 77-lb catfish that terrorized bathers at a German lake after swallowing a dachshund puppy whole, washes up dead; and after 20 days with no new case of SARS in Taiwan, the WHO declares the outbreak to be contained

Lifestyle, Diet & the Heart

Bibliography of One Hundred Key Papers

selected by **Scott M. Grundy, MD, PhD**

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-
- | | |
|--|---|
| Albert CM, Hennekens CH, O'Donnell CJ, et al. | <i>Fish consumption and risk of sudden cardiac death.</i>
JAMA. 1998;279:23-28. |
|--|---|
-
- | | |
|---|---|
| Alexander CM, Landsman PB, Teutsch SM, Haffner SM; National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). | <i>NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older.</i>
Diabetes. 2003;52:1210-1214. |
|---|---|
-
- | | |
|---|---|
| Almendingen K, Jordal O, Kierulf P, Sandstad B, Pedersen JI. | <i>Effects of partially hydrogenated fish oil, partially hydrogenated soybean oil, and butter on serum lipoproteins and Lp[a] in men.</i>
J Lipid Res. 1995;36:1370-1384. |
|---|---|
-
- | | |
|---|---|
| Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. | <i>The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers.</i>
N Engl J Med. 1994;330:1029-1035. |
|---|---|
-
- | | |
|--|---|
| American Diabetes Association Task Force for Writing Nutrition Principles and Recommendations for the Management of Diabetes and Related Complications. | <i>American Diabetes Association position statement: evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications.</i>
J Am Diet Assoc. 2002;102:109-118. |
|--|---|
-
- | | |
|-------------------------------|---|
| Anderson JW, Hanna TJ. | <i>Impact of nondigestible carbohydrates on serum lipoproteins and risk for cardiovascular disease.</i>
J Nutr. 1999;129:1457S-1466S. |
|-------------------------------|---|
-
- | | |
|---------------------|--|
| Anderson JW. | <i>Dietary fibre, complex carbohydrate and coronary artery disease.</i>
Can J Cardiol. 1995;11(suppl G):55G-62G. |
|---------------------|--|
-
- | | |
|---|--|
| Anderson P, Cremona A, Paton A, Turner C, Wallace P. | <i>The risk of alcohol.</i>
Addiction. 1993;88:1493-508. |
|---|--|
-
- | | |
|--|---|
| Appel LJ, Moore TJ, Obarzanek E, et al. | <i>A clinical trial of the effects of dietary patterns on blood pressure.</i>
N Engl J Med. 1997;336:1117-1124. |
|--|---|
-
- | | |
|--|--|
| Aro A, Jauhiainen M, Partanen R, Salminen I, Mutanen M. | <i>Stearic acid, trans-fatty acids, and dairy fat: effects on serum and lipoprotein lipids, apolipoproteins, lipoprotein(a), and lipid transfer proteins in healthy subjects.</i>
Am J Clin Nutr. 1997;65:1419-1426. |
|--|--|
-
- | | |
|--|--|
| Ascherio A, Katan MB, Zock PL, Stampfer MJ, Willett WC. | <i>Trans fatty acids and coronary heart disease.</i>
N Engl J Med. 1999;340:1994-1998. |
|--|--|
-

Bibliography of One Hundred Key Papers

- Ascherio A, Rimm EB, Stampfer MJ, Giovannucci EL, Willett WC.** *Dietary intake of marine n-3 fatty acids, fish intake, and risk of coronary disease among men.* **N Engl J Med.** 1995;332:977-982.
-
- Blot WJ, Li JY, Taylor PR, et al.** *Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population.* **J Natl Cancer Inst.** 1993;85:1483-1492.
-
- Bonanome A, Bennett M, Grundy SM.** *Metabolic effects of dietary stearic acid in mice: changes in the fatty acid composition of triglycerides and phospholipids in various tissues.* **Atherosclerosis.** 1992;94:119-127.
-
- Bonanome A, Grundy SM.** *Effect of dietary stearic acid on plasma cholesterol and lipoprotein levels.* **N Engl J Med.** 1988;318:1244-1248.
-
- Brown L, Rosner B, Willett WW, Sacks FM.** *Cholesterol-lowering effects of dietary fiber: a meta-analysis.* **Am J Clin Nutr.** 1999;69:30-42.
-
- Burr ML, Fehily AM, Gilbert JF, et al.** *Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: Diet and Reinfarction Trial (DART).* **Lancet.** 1989;2:757-761.
-
- Caggiula AW, Christakis G, Farrand M, et al, for the MRFIT.** *The Multiple Risk Intervention Trial (MRFIT). IV. Intervention on blood lipids.* **Prev Med.** 1981;10:443-475.
-
- Carroll S, Dudfield M.** *What is the relationship between exercise and metabolic abnormalities? A review of the metabolic syndrome.* **Sports Med.** 2004;34:371-418.
-
- Cater NB, Heller HJ, Denke M.** *Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans.* **Am J Clin Nutr.** 1997;65:41-45.
-
- Chobanian AV, Bakris GL, Black HR, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee.** *The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report.* **JAMA.** 2003;289:2560-2572.
-
- Criqui MH.** *Alcohol and coronary heart disease: consistent relationship and public health implications.* **Clin Chim Acta.** 1996;246:51-57.
-
- Daviglus ML, Stamler J, Orenca AJ, et al.** *Fish consumption and the 30-year risk of fatal myocardial infarction.* **N Engl J Med.** 1997;336:1046-1053.
-
- De Backer G, Ambrosioni E, Borch-Johnsen K, et al; Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice.** *European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice.* **Eur Heart J.** 2003;24:1601-1610.
-



-
- de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N.** *Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study.* **Circulation.** 1999;99:779-785.
-
- Denke MA, Grundy SM.** *Comparison of effects of lauric acid and palmitic acid on plasma lipids and lipoproteins.* **Am J Clin Nutr.** 1992;56:895-898.
-
- Diehl AM.** *Fatty liver, hypertension, and the metabolic syndrome.* **Gut.** 2004; 53:923-924.
-
- Dolecek TA, Grandits G.** *Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT).* **World Rev Nutr Diet.** 1991;66:205-216.
-
- Dufour MC.** *If you drink alcoholic beverages do so in moderation: what does this mean?* **J Nutr.** 2001;131(suppl):552S-561S.
-
- Fletcher GF, Balady G, Blair SN, Blumenthal J, et al.** *Statements on exercise: benefits and recommendations for physical activity programs for all Americans: a statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association.* **Circulation.** 1996;94:857-862.
-
- Garg A, Grundy SM, Unger RH.** *Comparison of effects of high and low carbohydrate diets on plasma lipoproteins and insulin sensitivity in patients with mild NIDDM.* **Diabetes.** 1992;41:1278-1285.
-
- Garg A.** *High-monounsaturated-fat diets for patients with diabetes mellitus: a meta-analysis.* **Am J Clin Nutr.** 1998;67(suppl):577S-582S.
-
- Ginsberg HN, Kris-Etherton P, Dennis B, et al, for the Delta Research Group.** *Effects of reducing dietary saturated fatty acids on plasma lipids and lipoproteins in healthy subjects: the Delta Study, Protocol I.* **Arterioscler Thromb Vasc Biol.** 1998;18:441-449.
-
- GISSI-Prevenzione Investigators.** *Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione Trial.* **Lancet.** 1999;354:447-455.
-
- Gordon DJ.** *Cholesterol and mortality: what can meta-analysis tell us? In: Gallo LL, ed. **Cardiovascular Disease 2: Cellular and Molecular Mechanisms, Prevention, and Treatment.** New York, NY: Plenum Press; 1995:333-340.*
-
- Gordon DJ.** *Cholesterol lowering and total mortality. In: Rifkind BM, ed. **Cholesterol in High-Risk Individuals and Populations.** New York: Marcel Dekker, Inc; 1995:333-348.*
-
- Gordon DJ.** *Cholesterol lowering reduces mortality: the statins. In: Grundy SM, ed. **Cholesterol-Lowering Therapy: Evaluation of Clinical Trial Evidence.** New York, NY: Marcel Dekker Inc; 2000:299-311.*
-

Bibliography of One Hundred Key Papers

- Grundy SM.** *Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol.*
N Engl J Med. 1986;314:745-748.
-
- Grundy SM.** *The optimal ratio of fat-to-carbohydrate in the diet.*
Annu Rev Nutr. 1999;19:325-341.
-
- Grundy SM.** *N-3 fatty acids: priority for post-myocardial infarction clinical trials.*
Circulation. 2003;107:1834-1836.
-
- Grundy SM, Barrett-Connor E, Rudel LL, Miettinen T, Spector AA.** *Workshop on the impact of dietary cholesterol on plasma lipoproteins and atherogenesis.*
Arteriosclerosis. 1988;8:95-101.
-
- Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C; American Heart Association; National Heart, Lung, and Blood Institute.** *Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition.*
Circulation. 2004;109:433-438.
-
- Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association.** *Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines.*
Circulation. 2004;110:227-239.
-
- Grundy SM, Denke MA.** *Dietary influences on serum lipids and lipoproteins.*
J Lipid Res. 1990;31:1149-1172.
-
- Gylling H, Miettinen TA.** *Cholesterol reduction by different plant stanol mixtures and with variable fat intake.*
Metabolism. 1999;48:575-580.
-
- Gylling H, Miettinen TA.** *Serum cholesterol and cholesterol and lipoprotein metabolism in hypercholesterolaemic NIDDM patients before and during sitostanol ester-margarine treatment.*
Diabetology. 1994;37:773-780.
-
- Gylling H, Radhakrishnan R, Miettinen TA.** *Reduction of serum cholesterol in postmenopausal women with previous myocardial infarction and cholesterol malabsorption induced by dietary sitostanol ester margarine: women and dietary sitostanol.*
Circulation. 1997;96:4226-4231.
-
- Gylling H, Siimes MA, Miettinen TA.** *Sitostanol ester margarine in dietary treatment of children with familial hypercholesterolemia.*
J Lipid Res. 1995;36:1807-1812.
-
- Hallikainen MA, Uusitupa MI.** *Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects.*
Am J Clin Nutr. 1999;69:403-410.
-
- Heart Outcomes Prevention Evaluation Study Investigators.** *Vitamin E supplementation and cardiovascular events in high-risk patients.*
N Engl J Med. 2000;342:154-160.
-
- Heart Protection Study Collaborative Group.** *MRC/BHF Heart Protection Study of antioxidant vitamin supplementation in 20,536 high-risk individuals: a randomised placebo-controlled trial.*
Lancet. 2002;360:23-33.
-



-
- Hendriks HFJ, Weststrate JA, van Vliet T, Meijer GW.** *Spreads enriched with three different levels of vegetable oil sterols and the degree of cholesterol lowering in normocholesterolaemic and mildly hypercholesterolaemic subjects.*
Eur J Clin Nutr. 1999;53:319-327.
-
- Hennekens CH, Buring JE, Manson JE, et al.** *Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease.*
N Engl J Med. 1996;334:1145-1149.
-
- Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA.** *Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis.*
Am J Clin Nutr. 1997;65:1747-1764.
-
- Hu FB, Stampfer MJ, Manson JE, et al.** *Dietary saturated fats and their food sources in relation to the risk of coronary heart disease in women.*
Am J Clin Nutr. 1999;70:1001-1008.
-
- Jenkins DJ, Kendall CW, Faulkner D, Vidgen E, Trautwein EA, Parker TL, Marchie A, Koumbridis G, Lapsley KG, Josse RG, Leiter LA, Connelly PW.** *A dietary portfolio approach to cholesterol reduction: combined effects of plant sterols, vegetable proteins, and viscous fibers in hypercholesterolemia.*
Metabolism. 2002;51:1596-604.
-
- Jenkins DJ, Kendall CW, Marchie A, et al.** *Effects of a dietary portfolio of cholesterol-lowering foods vs lovastatin on serum lipids and C-reactive protein.*
JAMA. 2003;290:502-510.
-
- Jenkins DJA, Wolever TMS, Rao AV, et al.** *Effect on blood lipids of very high intakes of fiber in diets low in saturated fat and cholesterol.*
N Engl J Med. 1993;329:21-26.
-
- Judd JT, Baer DJ, Clevidence BA, et al.** *Effects of margarine compared with those of butter on blood lipid profiles related to cardiovascular disease risk factors in normolipemic adults fed controlled diets.*
Am J Clin Nutr. 1998;68:768-777.
-
- Judd JT, Clevidence BA, Muesing RA, Wittes J, Sunkin ME, Podczasy JJ.** *Dietary trans fatty acids: effects on plasma lipids and lipoproteins of healthy men and women.*
Am J Clin Nutr. 1994;59:861-868.
-
- Kagan A, Harris BR, Winkelstein W Jr, et al.** *Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii, and California: demographic, physical, dietary and biochemical characteristics.*
J Chron Dis. 1974;27:345-364.
-
- Katan MB, Grundy SM, Jones P, Law M, Miettinen T, Paoletti R, Stresa Workshop Participants.** *Efficacy and safety of plant stanols and sterols in the management of blood cholesterol levels.*
Mayo Clin Proc. 2003;78:965-978.
-
- Katan MB, Zock PL, Mensink RP.** *Trans fatty acids and their effects on lipoproteins in humans.*
Ann Rev Nutr. 1995;15:473-493.
-
- Kendall CW, Jenkins DJ.** *A dietary portfolio: maximal reduction of low-density lipoprotein cholesterol with diet.*
Curr Atheroscler Rep. 1998;81:1497-1500.
-

Bibliography of One Hundred Key Papers

- Keys A, Arvanis C, Blackburn H.** *Seven countries: a multivariate analysis of death and coronary heart disease.* Cambridge, Mass: Harvard University Press; 1980;381.
-
- Keys A, Menotti A, Aravanis C, Blackburn H, et al.** *The Seven Countries Study: 2,289 deaths in 15 years.* **Prev Med.** 1984;13:141-154.
-
- Klein S.** *The case of visceral fat: argument for the defense.* **J Clin Invest.** 2004;113:1530-1532.
-
- Knuiman JT, West CE, Katan MB, Hautvast JG.** *Total cholesterol and high density lipoprotein cholesterol levels in populations differing in fat and carbohydrate intake.* **Arteriosclerosis.** 1987;7:612-619.
-
- Krauss RM, Eckel RH, Howard B, et al.** *AHA Dietary Guidelines: revision 2000: a statement for healthcare professionals from the Nutrition Committee of the American Heart Association.* **Circulation.** 2000;102:2284-2299.
-
- Kris-Etherton PM, Harris WS, Appel LJ; American Heart Association.** *Nutrition Committee. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease.* **Circulation.** 2002;106:2747-2757.
-
- Kris-Etherton PM, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD.** *High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations.* **Am J Clin Nutr.** 1999;70:1009-1015.
-
- Kris-Etherton PM, Yu S.** *Individual fatty acid effects on plasma lipids and lipoproteins: human studies.* **Am J Clin Nutr.** 1997;65(suppl 5):1628S-1644S.
-
- Kromhout D, Menotti A, Bloemberg B, et al.** *Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study.* **Prev Med.** 1995;24:308-315.
-
- Lakka HM, Laaksonen DE, Lakka TA, et al.** *The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men.* **JAMA.** 2002;288:2709-2716.
-
- Laughlin MH, McAllister RM, Jasperse JL, Crader SE, Williams DA, Huxley VH.** *Endothelium-mediated control of the coronary circulation. Exercise training-induced vascular adaptations.* **Sports Med.** 1996;22:228-250.
-
- Lichtenstein AH, Ausman LM, Carrasco W, Jenner JL, Ordovas JM, Schaefer EJ.** *Hydrogenation impairs the hypolipidemic effect of corn oil in humans: hydrogenation, trans fatty acids, and plasma lipids.* **Arterioscler Thromb.** 1993;13:154-161.
-
- Lichtenstein AH, Ausman LM, Jalbert SM, Schaefer EJ.** *Effects of different forms of dietary hydrogenated fats on serum lipoprotein cholesterol levels.* **N Engl J Med.** 1999;340:1933-1940.
-
- Lorenzo C, Okoloise M, Williams K, Stern MP, Haffner SM; San Antonio Heart Study.** *The metabolic syndrome as predictor of type 2 diabetes: the San Antonio heart study.* **Diabetes Care.** 2003;26:3153-3159.
-



-
- Mattson FH, Grundy SM.** *Comparison of effects of dietary saturated, monounsaturated, and polyunsaturated fatty acids on plasma lipids and lipoproteins in man.* **J Lipid Res.** 1985;26:194-202.
-
- Mensink RP, Katan MB.** *Effects of monounsaturated fatty acids versus complex carbohydrates on high-density lipoproteins in healthy men and women.* **Lancet.** 1987;1:122-125.
-
- Mensink RP, Katan MB.** *Effects of dietary trans fatty acids on high-density and low-density lipoprotein cholesterol levels in healthy subjects.* **N Engl J Med.** 1990;323:439-445.
-
- Mensink RP, Katan MB.** *Effects of dietary fatty acids on serum lipids and lipoproteins: a meta-analysis of 27 trials.* **Arterioscler Thromb.** 1992;12:911-919.
-
- Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E.** *Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population.* **N Engl J Med.** 1995;333:1308-1312.
-
- Morris MC, Manson JE, Rosner B, Buring JE, Willett WC, Hennekens CH.** *Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study.* **Am J Epidemiol.** 1995;142:166-175.
-
- National Institutes of Health.** *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults-The Evidence Report.* **Obes Res.** 1998;6(suppl 2):51S-209S.
-
- National Research Council.** *Diet and health: implications for reducing chronic disease risk.* Washington, DC: National Academy Press; 1989:171-201.
-
- National Research Council.** *Toxicological effects of methylmercury.* Washington, DC: National Academy Press; 1999.
-
- National Research Council.** *Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline.* Washington, DC: National Academy Press; 2000:1-567.
-
- National Research Council.** *Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids.* Washington, DC: National Academy Press; 2000:1-509.
-
- Nestle PJ, Noakes M, Belling GB, McArthur R, Clifton PM, Abbey M.** *Plasma cholesterol-lowering potential of edible-oil blends suitable for commercial use.* **Am J Clin Nutr.** 1992;55:46-50.
-
- Nielsen S, Guo Z, Johnson CM, Hensrud DD, Jensen MD.** *Splanchnic lipolysis in human obesity.* **J Clin Invest.** 2004;113:1582-1588.
-
- Niinikoski H, Lapinleimu H, Viikari J, et al.** *Growth until three years of age in a prospective randomized trial of a diet with reduced saturated fat and cholesterol.* **Pediatrics.** 1997;99:687-694.
-
- Ninomiya JK, L'Italien G, Criqui MH, et al.** *Association of the metabolic syndrome with history of myocardial infarction and stroke in the Third National Health and Nutrition Examination Survey.* **Circulation.** 2004;109:42-46.
-

Bibliography of One Hundred Key Papers

- Noakes M, Clifton PM. *Oil blends containing partially hydrogenated or interesterified fats: differential effects on plasma lipids.*
Am J Clin Nutr. 1998;68:242-247.
-
- Obarzanek E, Hunsberger SA, Van Horn L, et al. *Safety of a fat-reduced diet: the Dietary Intervention Study in Children (DISC).*
Pediatrics. 1997;100:51-59.
-
- Olijhoek JK, van der Graaf Y, Banga JD, Algra A, Rabelink TJ, Visseren FL; the SMART Study Group. *The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm.*
Eur Heart J. 2004;25:342-348.
-
- Omenn GS, Goodman GE, Thornquist MD, et al. *Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease.*
N Engl J Med. 1996;334:1150-1155.
-
- Pearson TA, Blair SN, Daniels SR, et al. *AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee.*
Circulation. 2002;106:388-391.
-
- Pietinen P, Ascherio A, Korhonen P, et al. *Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study.*
Am J Epidemiol. 1997;145:876-887.
-
- Purnell JQ, Kahn SE, Albers JJ, Nevin DN, Brunzell JD, Schwartz RS. *Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men.*
J Clin Endocrinol Metab. 2000;85:977-982.
-
- Ridker PM, Wilson PW, Grundy SM. *Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk?*
Circulation. 2004;109:2818-2825.
-
- Rimm EB, Klatsky A, Grobbee D, Stampfer MJ. *Review of moderate alcohol consumption and reduced risk of coronary heart disease: is the effect due to beer, wine or spirits?*
BMJ. 1996;312:731-736.
-
- Rimm EB, Williams P, Fosher K, Criqui M, Stampfer MJ. *Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors.*
BMJ. 1999;319:1523-1528.
-
- Sacks FM, Svetkey LP, Vollmer WM, et al, for the DASH-Sodium Collaborative Research Group. *Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet.*
N Engl J Med. 2001;344:3-10.
-
- Sesso HD. *Alcohol and cardiovascular health: recent findings.*
Am J Cardiovasc Drugs. 2001;1:167-172.
-
- Singh RB, Niaz MA, Sharma JP, Kumar R, Rastogi V, Moshiri M. *Randomized, double-blind, placebo-controlled trial of fish oil and mustard oil in patients with suspected acute myocardial infarction: the Indian Experiment of Infarct survival-4.*
Cardiovasc Drugs Ther. 1997;11:485-491.
-



-
- Stamler J, Briefel RR, Milas C, Grandits GA, Caggiula AW.** *Relation of changes in dietary lipids and weight, trial years 1-6, to change in blood lipids in the special intervention and usual care groups in the Multiple Risk Factor Intervention Trial.*
Am J Clin Nutr. 1997;65(suppl):272S-288S.
-
- Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ.** *Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS).*
Lancet. 1996;347:781-786.
-
- Third report of the National Cholesterol Education Program (NCEP) expert panel.** *On detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). Final Report.*
Circulation. 2002;106:3143-3421.
-
- Tippett KS, Cleveland LE.** *How current diets stack up: comparison with dietary guidelines. In: America's eating habits: changes and consequences. Washington, DC: United States Department of Agriculture, Economic Research Service; 1999:51-70.*
-
- US Department of Agriculture and US Department of Health and Human Services.** *Nutrition and your health: dietary guidelines for Americans, 5th edition.*
Home and Garden Bulletin no. 232. Washington, DC: US Department of Agriculture; 2000;44.
-
- US Department of Health and Human Services.** *Physical Activity and Health: A Report of the Surgeon General. Atlanta, Georgia: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion; 1996:1-278.*
-
- US Department of Health and Human Services.** *Food and Drug Administration. Food labeling: health claims; soluble fiber from certain foods and coronary heart disease: proposed rule.*
Fed Reg. 1997;62:28234-28245.
-
- US Department of Health and Human Services.** *Food and Drug Administration. Food labeling: health claims; soluble fiber from certain foods and coronary heart disease: final rule.*
Fed Reg. 1998;63:8103-8121.
-
- US Department of Health and Human Services.** *Food and Drug Administration. Food labeling: health claims; soy protein and coronary heart disease: proposed rule.*
Fed Reg. 1998;63:62977-63015.
-
- Vanhanen HT, Blomqvist S, Ehnholm C, et al.** *Serum cholesterol, cholesterol precursors, and plant sterols in hypercholesterolemic subjects with different apoE phenotypes during dietary sitostanol ester treatment.*
J Lipid Res. 1993;34:1535-1544.
-
- Vuksan V, Sievenpiper JL, Owen R, et al.** *Beneficial effects of viscous dietary fiber from Konjac-mannan in subjects with the insulin resistance syndrome: results of a controlled metabolic trial.*
Diabetes Care. 2000;23:9-14.
-
- Vuorio AF, Gylling H, Turtola H, Kontula K, Ketonen P, Miettinen TA.** *Stanol ester margarine alone and with simvastatin lowers serum cholesterol in families with familial hypercholesterolemia caused by the FH-North Karelia mutation.*
Arterioscler Thromb Vasc Biol. 2000;20:500-506.
-

Bibliography of One Hundred Key Papers

- Walden CE, Retzlaff BM, Buck BL, McCann BS, Knopp RH.** *Lipoprotein lipid response to the National Cholesterol Education Program Step II diet by hypercholesterolemic and combined hyperlipidemic women and men.*
Arterioscler Thromb Vasc Biol. 1997;17:375-382.
-
- Walden CE, Retzlaff BM, Buck BL, Wallick S, McCann BS, Knopp RH.** *Differential effect of National Cholesterol Education Program (NCEP) Step II diet on HDL cholesterol, its subfractions, and apoprotein A-I in hypercholesterolemic women and men after 1 year: the beFIT study.*
Arterioscler Thromb Vasc Biol. 2000;20:1580-1587.
-
- Weggemans RM, Zock PL, Katan MB.** *Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis.*
Am J Clin Nutr. 2001;73:885-891.
-
- West CE, Sullivan DR, Katan MB, Halferkamp IL.** *Boys from populations with high-carbohydrate intake have higher fasting triglyceride levels than boys from populations with high-fat intake.*
Am J Epidemiol. 1990;131:271-282.
-
- Westrate JA, Meijer GW.** *Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normocholesterolaemic and mildly hypercholesterolaemic subjects.*
Eur J Clin Nutr. 1998;52:334-343.
-
- Willett WC, Stampfer MJ, Manson JE, et al.** *Intake of trans fatty acids and risk of coronary heart disease among women.*
Lancet. 1993;341:581-585.
-
- Wilson PW.** *Estimating cardiovascular disease risk and the metabolic syndrome: a Framingham view.*
Endocrinol Metab Clin North Am. 2004; 33:467-481.
-
- Wood R, Kubena K, O'Brien B, Tseng S, Martin G.** *Effect of butter, mono- and polyunsaturated fatty acid-enriched butter, trans fatty acid margarine, and zero trans fatty acid margarine on serum lipids and lipoproteins in healthy men.*
J Lipid Res. 1993;34:1-11.
-
- Wood R, Kubena K, Tseng S, Martin G, Crook R.** *Effect of palm oil, margarine, butter, and sunflower oil on the serum lipids and lipoproteins of normocholesterolemic middle-aged men.*
J Nutr Biochem. 1993;4:286-297.
-
- Zock PL, de Vries JH, Katan MB.** *Impact of myristic acid versus palmitic acid on serum lipid and lipoprotein levels in healthy women and men.*
Arterioscler Thromb. 1994;14:567-575.
-
- Zock PL, Katan MB.** *Hydrogenation alternatives: effects of trans fatty acids and stearic acid versus linoleic acid on serum lipids and lipoproteins in humans.*
J Lipid Res. 1992;33:399-410.
-

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