The Cholesterol Facts
A Summary of the Evidence Relating Dietary Fats, Serum Cholesterol, and Coronary Heart Disease

A Joint Statement by the American Heart Association and the National Heart, Lung, and Blood Institute

Commissioned by the Task Force on Cholesterol Issues, American Heart Association

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The efforts of the National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) to inform the public about the role of cholesterol in coronary heart disease (CHD) have recently come under criticism. The critics, popular magazine writers and a small group of physicians, suggest that the relation between cholesterol and CHD is not well defined, that lowering serum cholesterol does not extend life, that low-saturated fat, low-cholesterol diets do little to reduce risk of CHD, and that lowering cholesterol levels is a waste of time and money. These comments have prompted some patients to question the need to adopt a lifestyle that includes a diet aimed at lowering serum cholesterol levels.

The AHA and the National Heart, Lung, and Blood Institute (NHLBI) intend to remove doubts about the direct link between cholesterol and CHD. This statement reviews the epidemiologic, laboratory, and clinical studies that address questions most frequently asked about cholesterol: Is high serum cholesterol a risk factor for coronary heart disease? Will lowering serum cholesterol help prevent coronary heart disease? Will people live longer if their serum cholesterol levels are modified? Does management of high serum cholesterol provide benefit if coronary heart disease is already present? Will dietary change effectively lower cholesterol levels? Should age or gender change the approach to cholesterol management? Are cholesterol interventions cost-effective?

Is High Serum Cholesterol a Risk Factor for Coronary Heart Disease?

Will Lowering Serum Cholesterol Help Prevent Coronary Heart Disease?

Strong scientific data provide positive answers to both of these questions. The evidence linking elevated serum cholesterol to CHD is overwhelming. Epidemiologic, clinical, genetic, and laboratory animal studies all indicate that high serum levels of cholesterol are causally related to coronary atherosclerosis and increased risk of CHD. The epidemiologic evidence includes comparisons among various populations and prospective studies within popula-
tions. In both types of studies, the predictive connection between serum cholesterol levels and future occurrence of CHD is continuous and positive throughout the range of cholesterol levels typically found in the United States. Moreover, in individuals with genetic forms of hypercholesterolemia, premature CHD commonly occurs even in the absence of other risk factors.

Many animal species, including monkeys and baboons, develop atherosclerosis when fed diets that raise serum cholesterol levels. In monkeys, severe atherosclerotic lesions regress when serum cholesterol levels are substantially lowered by diet or drugs.

Clinical trials in humans have shown that lowering levels of serum cholesterol with diet or drugs decreases the subsequent incidence of fatal or nonfatal CHD. Direct evidence of benefits of cholesterol lowering obtained through clinical trials is strongest for middle-aged men with initially high serum cholesterol levels. However, the complete set of evidence, including that from epidemiologic studies and experiments in animals, strongly suggests that reducing cholesterol levels will decrease incidence of CHD in younger and older men, in women, and in persons with more moderate elevations of serum cholesterol.

The large body of evidence on these questions was reviewed comprehensively in the recent report on diet and health from the National Research Council—National Academy of Sciences.1 The report cites the many studies showing a powerful link between cholesterol and CHD. These studies are too numerous to review in detail; therefore, this statement highlights some of the key reports that confirm the link. (See Bibliography for a more complete listing of research reviewed in the Diet and Health report.) The following are among the most prominent of those studies:

- Framingham Heart Study
- Multiple Risk Factor Intervention Trial
- Brown and Goldstein’s research on low-density lipoprotein (LDL) receptors
- Coronary Primary Prevention Trial
- Helsinki Heart Study

The Framingham Heart Study, which began 40 years ago and is ongoing, provided early epidemiologic evidence that elevated serum cholesterol is a risk factor for CHD.2 In 1971, investigators reported the cholesterol and coronary histories of 2,282 men and 2,845 women in Framingham, Massachusetts, over a period of 14 years. During this study, almost all of the Framingham participants had total serum cholesterol levels between 150 and 300 mg/dl. Investigators found a positive correlation between serum cholesterol levels and CHD rates across the range of cholesterol measurements (Figure 1). Low levels of serum cholesterol were associated with low rates of CHD, while high levels of serum cholesterol were associated with high rates of CHD.

![Relationship Between Total Cholesterol and Incidence of Coronary Heart Disease](image1)

**Figure 1.** Adapted from Framingham Study, 1971.

The Multiple Risk Factor Intervention Trial (MRFIT), a randomized, primary prevention trial, tested the effects of modifying several coronary risk factors in 12,866 high-risk men, aged 35–57, selected from a cohort of more than 360,000 middle-aged men.3 The serum cholesterol levels of the larger cohort were measured and the CHD death rate over the next 6 years was observed, providing extraordinary epidemiologic data on the relation between higher cholesterol levels and increased risk of CHD. In fact, the data showed that the association between elevated serum cholesterol and increased CHD mortality begins with serum cholesterol levels as low as 180 mg/dl (Figure 2).

In 1985, Doctors Michael Brown and Joseph Goldstein were awarded the Nobel Prize in Medicine or Physiology for their investigations on cell surface
proteins that they named low-density lipoprotein receptors, or LDL receptors. The two investigators noted that individuals with a deficiency or absence of LDL receptors are prone to atherosclerosis and premature CHD. They observed that LDL receptors are needed to help transfer the body's atherogenic LDL particles to the liver for excretion. However, a diet rich in cholesterol and saturated fatty acids apparently signals the body to manufacture fewer LDL receptors. Doctors Brown and Goldstein suggest that lifestyle-induced deficiency of LDL receptors results in an increased LDL concentration and a greater risk of CHD.

Evidence that reducing high levels of serum cholesterol will decrease risk of CHD was provided by the Lipid Research Clinics Coronary Primary Prevention Trial (CPPT). More than 3,800 hypercholesterolemic, middle-aged men participated in this double-blind trial. The men were placed on cholesterol-lowering diets to reduce their serum cholesterol levels by about 4%. The men were then randomized and treated with either a placebo or the bile acid sequestrant cholestyramine. Since cholestyramine is a bulky substance that can cause indigestion and constipation, most men in the cholestyramine group took less than the 24 g/day prescribed. Nonetheless, over the 7-year trial period, subjects in the cholestyramine group had reductions in total serum cholesterol that were, on average, 9% greater than those experienced in the placebo group. The cholestyramine group also had 19% fewer coronary events than the placebo group, a reduction that was statistically significant. These events included CHD death and nonfatal myocardial infarction. Moreover, subjects who took the full dose of medication reduced their serum cholesterol levels by 25% and experienced almost 50% fewer coronary events than the placebo group.

The CPPT results and those from the Framingham Study indicate that a 1% reduction in an individual's total serum cholesterol level translates into an approximate 2% reduction in CHD risk. However, the relation of cholesterol lowering to reduced CHD risk may be even stronger than the 1:2 ratio suggested by these studies. Richard Peto of Oxford University analyzed the results of 18 published and two unpublished randomized trials of cholesterol lowering by diet or drugs and concluded that a 1% reduction of total serum cholesterol over decades would translate into a 3% reduction in CHD risk.

Like the CPPT results, the findings reported in 1987 of a clinical trial, the Helsinki Heart Study, also showed that drug treatment to lower elevated levels of serum cholesterol reduces risk of CHD. The 2,051 Helsinki patients treated with the fibrin acid derivative gemfibrozil lowered their total and LDL-cholesterol levels by an average of 8% and raised their high-density lipoprotein (HDL) cholesterol levels by an average of 10%. In this study, the men in the gemfibrozil group had 34% fewer coronary events than the 2,030 men in the placebo group. The results of this trial suggest that in addition to the established benefit gained by lowering total cholesterol and LDL cholesterol, further benefit was gained by raising HDL cholesterol. The apparent protective effect of elevated HDL-cholesterol levels has also been found in the CPPT and the Framingham Study as well as other epidemiologic studies.

Will People Live Longer If Their Serum Cholesterol Levels Are Modified?

Critics of the national cholesterol program, who may concede the relation of elevated serum cholesterol to CHD risk, nonetheless claim there is no evidence that lowering serum cholesterol will reduce overall death rates. In particular, they point to the lack of such evidence in the CPPT and the Helsinki Heart Study.

The fact is that these two major clinical trials were not designed to demonstrate a reduction in total mortality, but only a reduction in incidence of total CHD, as measured by fatal and nonfatal CHD events. Since most CHD events are not fatal, these trials would have needed to be larger or longer in duration, or both, to demonstrate an effect on total mortality.

Evidence from epidemiologic studies strongly suggests that low serum cholesterol levels are accompanied by prolongation of life. In countries under investigation in the Seven Countries Study, those individuals with the lowest average levels of serum cholesterol have the greatest life expectancy. Moreover, in the 30-year follow-up of the Framingham Heart Study, individuals with higher cholesterol levels died at an earlier age, while those with lower cholesterol levels lived longer.

A reduction in total mortality, moreover, was reported in three recent clinical studies:

- The Coronary Drug Project
- Oslo Study Diet and Antismoking Trial
- Stockholm Ischemic Heart Disease Study

The Coronary Drug Project of the NHLBI was a placebo-controlled, double-blind study of male heart attack survivors conducted in the 1960s and 1970s. For 6 years, the men were treated with a lipid-lowering drug or placebo. By the end of the treatment period, the 1,119 men who received nicotinic acid had significantly lowered average levels of total serum cholesterol, LDL, very low-density lipoprotein (VLDL), triglycerides, and increased HDL levels. Moreover, these men had experienced 29% fewer heart attacks than the 2,789 men in the placebo group. A difference in overall mortality was evident 9 years later. A follow-up report at that time showed that the nicotinic acid group had experienced 11% fewer deaths than the placebo group, and this difference was statistically significant.

As with the Coronary Drug Project, a long-term follow-up of the Oslo Study Diet and Antismoking
Trial was needed before the effects of lipid modification on overall mortality were evident. The 1,200 healthy men in the Oslo Trial were randomized either to a control or intervention group. By the end of the 5-year trial period, total serum cholesterol levels for the intervention group were reduced by an average of 13% with diet alone, compared with only 3% in the control group. At this time, the incidence of clinical CHD events, which included fatal and nonfatal myocardial infarction and sudden death, was 47% lower in the intervention group than in the control group.

A follow-up 3–4 years after completion of the trial showed that these trends had continued; the intervention group had experienced 45% fewer CHD events than the placebo group. The difference between the number of deaths in both groups had also widened by the time of the follow-up survey. At the 5-year mark, the intervention group had experienced 33% fewer deaths from all causes than the control group; at the 8- to 9-year mark, the difference was 40%.

All 555 participants in the Stockholm Ischemic Heart Disease Study suffered a heart attack no more than 3 months before the start of the study. Their particularly high coronary risk allowed Swedish investigators to analyze the effects of lipid modification on overall mortality over the 5-year period of the study. The Stockholm participants were randomized into a control group or a group given a combined treatment of clofibrate and nicotinic acid. By the end of the study period, total serum cholesterol and triglyceride levels of the treated group had been lowered by 13% and 19%, compared with the control group. The treated group had also experienced 26% fewer deaths than the control group, with 36% fewer deaths due to ischemic heart disease.

Critics have been so preoccupied with total mortality that they often overlook an important point: A reduction in total mortality may not be the best indicator of the value of serum cholesterol lowering. By preventing the occurrence of nonfatal heart attacks, incidence and prevalence of chronic CHD is reduced. Approximately 5 million Americans are living and suffering from CHD. By decreasing this number, the quality of life for millions of Americans can be improved, regardless of whether they live longer. Thus, an important goal of a cholesterol reduction program should be to prevent CHD and, by doing so, improve the quality of life.

Does Management of High Serum Cholesterol Provide Benefit If Coronary Heart Disease Is Already Present?

The clinical trials and epidemiologic data discussed above show that lowering of serum cholesterol levels reduces risk of CHD and even decreases overall mortality. The Coronary Drug Project, in particular, also indicated that lipid modification was beneficial for individuals who already had CHD. As described earlier, the nicotinic acid-treated group of heart attack survivors experienced fewer recurring heart attacks and fewer deaths than the placebo group.

Several animal studies and three recent clinical trials provide additional information about the benefits of cholesterol lowering. These studies indicate that a favorable modification of serum lipoproteins can slow the progression of coronary atherosclerotic plaque and, in some cases, induce regression of atherosclerosis.

One animal study that demonstrated reversal of atherosclerosis was reported in 1983. Monkeys were fed an atherogenic diet for 20 months, then a nonatherogenic diet without cholesterol for another 18 months. By the end of the test period, the diet without cholesterol led to a greater than 50% reduction of size of atherosclerotic plaques in coronary arteries.

Two clinical studies linked favorable modification of lipoproteins to retardation or regression of atherosclerotic plaque in humans:

- NHLBI Type II Coronary Intervention Study
- Cholesterol Lowering Atherosclerosis Study

The 116 patients in the NHLBI Type II Coronary Intervention Study had type II hyperlipoproteinemia, coronary artery disease, or both at the start of the trial. The patients were initially put on a low saturated fat, low-cholesterol diet that lowered their LDL levels by 6%. They were then randomized into a drug-treatment or placebo group. The former was treated with a total daily dose of 24 g cholestyramine for 5 years. By the end of the study period, LDL-cholesterol levels had fallen another 5% in the placebo group and an additional 26% in the cholestyramine group. Coronary angiography was performed before and after the 5 years of treatment. Posttreatment angiograms indicated that coronary artery disease had progressed in 49% of placebo-treated patients versus 32% of cholestyramine-treated patients. This difference was statistically significant.

The Cholesterol Lowering Atherosclerosis Study (CLAS) included 162 men who had recently undergone coronary artery bypass surgery. At the start of the study, their levels of total serum cholesterol ranged from 180 to 350 mg/dl. The men were divided into two groups. The first group received only dietary treatment. The second group received a more intensive dietary treatment plus mean daily doses of 4.5 g nicotinic acid and 29.5 g colestipol. Coronary arteriography was used to assess the condition of the men's native vessels and bypass grafts at the start of the study and 2 years after treatment. Investigators calculated global coronary artery scores, which rate overall progression or regression of lesions present in the original angiogram. Regression of coronary atherosclerosis occurred in 16.2% of the group that received diet plus drug treatment, compared with 2.4% of the group who received only dietary treatment. Results also demonstrated that 61% of the...
drug-treatment group showed either regression or no change in coronary atherosclerosis, compared with only 39% of the placebo group.

Another smaller study, the Leiden Intervention Trial of 39 patients in The Netherlands, had angiographic evidence of coronary artery disease before intervention.\textsuperscript{16} Intervention in this trial consisted of a 2-year vegetarian diet with twice as many polyunsaturated to saturated fatty acids and less than 100 mg cholesterol per day. Angiograms taken after the 2-year period indicated that 46% of the patients had not experienced lesion progression. Investigators noted that these patients had low ratios of total serum cholesterol to HDL cholesterol throughout the trial or had significantly lowered these ratios through dietary treatment.

The results of a 2-year extension of the Cholesterol Lowering Atherosclerosis Study were released during the AHA's 62nd Scientific Sessions in November 1989.\textsuperscript{17} Those treated with colestipol and nicotinic acid for 4 years continued to benefit during the extension period. When a new set of global coronary artery scores was compared with the older scores, additional atherosclerotic regression was evident in 17.9% of the drug-treatment group, as opposed to 6.4% of the placebo group.

The initial results of a fourth study on atherosclerotic regression were also released during the 62nd Scientific Sessions.\textsuperscript{18} Results of the Familial Atherosclerosis Treatment Study (FATS) provide further evidence that favorable modification of serum lipoproteins by drug therapy can cause regression of coronary atherosclerosis.

**Will Dietary Change Effectively Lower Cholesterol Levels?**

Some critics have suggested that dietary change has little effect on serum cholesterol levels and thus cannot significantly reduce risk for CHD. They frequently point out that a definitive trial of serum cholesterol reduction by diet and its effect on CHD has never been conducted.

In 1968, the Arteriosclerosis Task Force of the National Heart Institute decided against such a trial because of several potential problems, including the near impossibility of maintaining a blind study of diet with a large group of participants over a long-term period, the probable mobility of the participants, and the difficulty of recruiting a control group to ingest a constant diet for many years.\textsuperscript{19} Cost, which was projected to be huge, was another limiting factor. It is unlikely that such a study will be done.

Nevertheless, the absence of a large-scale diet-heart trial does not negate the substantial evidence from laboratory, epidemiologic, and clinical studies of the role of diet in atherosclerosis and CHD. This large body of evidence shows the powerful link between diet and CHD, and that diet is a significant determinant of a person's serum cholesterol level. This evidence is reviewed in full in the National Research Council Diet and Health report.\textsuperscript{1} The report concluded that high intakes of saturated fatty acids, cholesterol, and excess calories leading to obesity are causally related to atherosclerotic cardiovascular disease.

Seven epidemiologic studies showing the link between diet and CHD have produced particularly impressive results:

- Seven Countries Study
- Japan-Honolulu-San Francisco Study
- Zutphen Study
- Honolulu Heart Program
- Ireland-Boston Study
- Western Electric Study
- United Nations Food and Agriculture Organization Study

According to these and many other epidemiologic studies, three major dietary factors influence a person's risk of CHD. These factors are dietary saturated fatty acids, dietary cholesterol, and obesity.

**Dietary Saturated Fatty Acids**

The Seven Countries Study provides the strongest evidence that diets high in saturated fatty acids increase the risk of CHD.\textsuperscript{20} This 15-year study recorded the clinical histories of a total of 11,579 middle-aged men in Finland, Greece, Italy, Japan, The Netherlands, the United States, and Yugoslavia. During the study, the men were examined every 5 years for a number of coronary risk factors, including hypertension, hypercholesterolemia, and smoking. Detailed analyses of their diets were also conducted.

The study's 5- and 10-year surveys indicated a strong, independent correlation between the men's consumption of saturated fatty acids and their rates of CHD. The same results were noted in the 15-year follow-up survey, but this time, the men's consumption of saturated fatty acids was also correlated with their total mortality rates.\textsuperscript{21}

The Japan-Honolulu-San Francisco Study is another epidemiologic trial showing a strong correlation between dietary saturated fatty acids and CHD.\textsuperscript{22} In this study, investigators recorded the dietary habits and coronary histories of three groups of Japanese men. Men in the first group were born in Japan and continued to live there throughout the study. Their diet was low in saturated fat and cholesterol. Men in the second group were native Japanese who had moved to Hawaii and adopted a local diet rich in saturated fat and cholesterol. The third group was composed of native Japanese who had moved to California and adopted a local diet that was still richer in saturated fat and cholesterol. The men's dietary habits were reflected in their serum cholesterol levels and their rates of CHD: Japanese men who remained in their native country had low rates of CHD, whereas Japanese men who moved to Hawaii and California had progressively higher serum cholesterol levels and rates of CHD.
Still other epidemiologic studies showing a correlation between saturated fatty acids and CHD include the Honolulu Heart Program, the Ireland-Boston Study, the Western Electric Study, the Zutphen Study, and the United Nations' Food and Agriculture Organization Study of CHD rates in 20 countries (see Bibliography).

In addition to these epidemiologic studies, clinical studies in metabolic wards have clearly shown that dietary saturated fatty acids raise serum total and LDL-cholesterol levels. These studies show that substitution of saturated fatty acids for any other nutrient—carbohydrates, monounsaturated, or polyunsaturated fatty acids—will consistently raise serum cholesterol by a predictable amount. The extent of this increase has been well defined by many quantitative investigations. The reverse is also true; replacement of saturated fat by any of these nutrients lowers serum cholesterol levels.

**Dietary Cholesterol**

The effects of dietary cholesterol on development of atherosclerosis in animal models is well documented. One of the most relevant studies was conducted in the early 1980s. In this study, a diet high in cholesterol was used to develop two stages of severity of atherosclerosis in rhesus monkeys. The first stage was comparable to atherosclerosis in 35-year-old men; the second stage to atherosclerosis of 50-year-old men. Once the appropriate stages of atherosclerosis were reached, the monkeys were fed a diet lower in cholesterol, which reduced their serum cholesterol concentrations to levels of 180–200 mg/dl, 201–220 mg/dl, and above 220 mg/dl. This dietary treatment continued for 4 years. By the end of that period, monkeys with cholesterol levels in the higher ranges had very slight regression in coronary lesions, but monkeys with serum cholesterol levels in the lowest range had considerable regression of coronary lesions.

It has also been found that dietary cholesterol will raise serum cholesterol levels in humans. As with saturated fatty acids, the response to dietary cholesterol has been quantitatively defined in many metabolic ward investigations. There is much interindividual and intraindividual variability in this response. However, these studies clearly show that high intakes of dietary cholesterol will significantly raise serum cholesterol levels in the majority of people.

Epidemiologic studies that show a strong, independent correlation between consumption of dietary cholesterol and risk of CHD in humans include the Honolulu Heart Study, the Ireland-Boston Study, the Zutphen Study, and the Western Electric Study.

The Western Electric Study began in 1958 with dietary and clinical examinations of more than 1,900 middle-aged men. The men were reexamined annually for the next 19 years. Detailed dietary histories were taken at the start of the study and at the first reexamination in 1959. It should be noted that the men's dietary habits were not assessed by simple 24-hour recall questionnaires. Instead, the researchers conducted month-long interviews with the men to assess their long-term nutrient consumption. The 19-year follow-up of these men revealed an independent correlation between average daily consumption of dietary cholesterol and rates of CHD. Furthermore, follow-up indicated that a habitual reduction of 200 mg cholesterol/1,000 kcal was associated with a 37% reduction in total mortality or an increase in life expectancy of 3.4 years.

Studies by the United Nations' Food and Agriculture Organization and the World Health Organization also link dietary cholesterol to mortality rates. Details of these and other relevant epidemiologic studies are extensively reviewed in a report by Stabler and Shekelle, and in the National Research Council report on Diet and Health.

**Obesity**

Several reports indicate a connection between obesity and CHD. The reasons for this connection are not clear because obesity has many different metabolic effects: it raises blood pressure, increases serum cholesterol, induces glucose intolerance, and is associated with reduced HDL levels. Since each of these factors can increase the risk of CHD, the influence of obesity might be explained by its action on these known factors.

On the other hand, data from the ongoing Framingham Heart Study indicate that obesity is also an independent risk factor for CHD. Investigators examined the relation between the degree of obesity and incidence of cardiovascular disease in a total of 5,209 men and women from the original study cohort. These individuals were followed for 26 years with their weights charted against the Metropolitan Relative Weight Tables. Investigators found that an individual's percentage of desirable weight at the first examination was a predictor of his or her coronary history 26 years later. This correlation was independent of age, serum cholesterol, blood pressure, cigarette smoking, left ventricular hypertrophy, and glucose intolerance. Moreover, weight gain after the initial examination was also a predictor of increased risk of CHD.

When the influence of all three cholesterol-raising factors—saturated fatty acids, dietary cholesterol, and obesity—is considered, it is estimated that most Americans can reduce their serum cholesterol levels by about 10% by adopting the diet recommended by the AHA. This translates into a reduction in CHD of approximately 20%. A sizeable portion of the population, particularly those with high serum cholesterol levels, can reduce their levels by well over 10%, producing an even greater reduction in CHD risk. Thus, it is clear that dietary modification can make a difference by reducing serum cholesterol and CHD risk.

In summary, a large and substantial body of evidence supports a direct relation between diet and risk of CHD. Accordingly, virtually every major medical or
health organization has urged Americans to decrease their consumption of saturated fat, to lower their consumption of cholesterol, and to lose excess weight. These organizations include the American Heart Association, the Population Panel of the National Cholesterol Education Program, the American Medical Association, the Food and Nutrition Board of the Institute of Medicine and the National Academy of Science, the Surgeon General’s Office, and many health organizations abroad.

**Should Age or Gender Change the Approach to Cholesterol Management?**

**Women and Cholesterol**

The majority of cholesterol studies, including most major intervention trials, have focused primarily on men. One reason is that men develop CHD, on average, 10–15 years earlier than women. Men often develop CHD in their 50s and 60s, whereas women are more affected in their late 60s and 70s, after menopause. Another reason is that the cost of a trial focusing on women would be much greater, given the lower absolute risk of CHD in women at any age. Clinical trials involving men are very expensive, costing millions of dollars; comparable trials involving women would be even more costly.

Critics suggest that the NCEP guidelines should not be extended to women until results of clinical trials of cholesterol modification in women are in hand. This suggestion, however, ignores both extensive data from epidemiologic studies that link elevated serum cholesterol levels in women to increased CHD risk and data from dietary studies showing that women, as well as men, can lower their serum cholesterol levels through diet. Although women tend to develop CHD at a later age than men, nearly as many women as men die of it. In fact, CHD is the number one killer of American women, accounting for nearly 250,000 deaths annually. More women die of circulatory disease than from all forms of cancer, including breast cancer, ovarian cancer, and cervical cancer combined (Figure 3). Finally, it should be noted that the atherosclerotic pathologic process appears to be the same in women as in men, and that LDL (particularly elevated LDL) is critical for development of coronary atherosclerosis.

Epidemiologic studies have indicated that women share the same major CHD risk factors as men, including elevated serum cholesterol levels, and have additional risks unique to their gender. For example, the Framingham Study revealed that diabetes may be an even more potent coronary risk factor for women than men, and that elevated triglycerides may be a risk factor for women only. Other studies indicate that women’s risk of CHD may be altered by natural or surgical menopause, use of oral contraceptives, and hormone replacement therapy. In particular, researchers have noted that after menopause, a woman’s body produces far less estrogen. This reduction in estrogen apparently contributes to the substantial increase in older women’s LDL-cholesterol levels and the subsequent surge in CHD among postmenopausal women.

At least nine epidemiologic and dietary studies provide evidence that women will benefit from the cholesterol management guidelines recommended for both sexes by the NCEP. Among these studies are the following:

- Framingham Heart Study
- Lipid Research Clinics Program Follow-up Study
- Rancho Bernardo Study
- Tecumseh Study
- Charleston Study
- Evans County Study
- Donolo-Tel Aviv Study
- Nurses Study
- Gothenburg Study

Table 1 reviews the outcome of this research. While not all study results indicated a statistically significant correlation between total serum cholesterol and CHD in women, certain important trends are evident. For example, the studies demonstrated that women tend to develop CHD at higher cholesterol levels than men. Coronary risk was accelerated in women with total serum cholesterol levels above 265 mg/dl in the Framingham and Donolo-Tel Aviv studies and in women with total serum cholesterol levels above 235 mg/dl in the Lipid Research Clinics Program Follow-up Study. These findings may reflect the fact that HDL cholesterol comprises a greater proportion of a woman’s total serum cholesterol concentration. Indeed, the inverse correlation between HDL and CHD is especially strong in women; a decrease of 10 mg/dl induced a 50% increase in coronary risk among the Framingham women and a 42% increase in risk among the women of the Lipid Research Clinics follow-up.

The data from these epidemiologic and dietary studies are more than sufficient to justify use of the NCEP cholesterol management guidelines in women.

**The Elderly and Cholesterol**

Absolute rates of CHD are high among the elderly, and CHD is the principal cause of death in people over 65. In fact, CHD mortality rates in the 65 and

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**Figure 3.** Cardiovascular disease is the leading cause of death in American women. Adapted from Castelli. Reproduced with permission.
TABLE 1. Summary of Prospective Studies in Women: Cholesterol and Lipoproteins as Predictors of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Lipid/lipoprotein</th>
<th>Statistically significant*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Framingham</td>
<td>Cholesterol</td>
<td>Yes</td>
<td>Clear elevations of risk not seen at (&lt;265) mg/dl</td>
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<tr>
<td></td>
<td>HDL</td>
<td>Yes</td>
<td>A 10 mg/dl change results in a 50% change in risk; major lipid risk factor</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>Yes</td>
<td>Less powerful a predictor than HDL</td>
</tr>
<tr>
<td>Lipid Research Clinics</td>
<td>Cholesterol</td>
<td>No</td>
<td>Risk of death 70% higher in women with (&gt;235) mg/dl</td>
</tr>
<tr>
<td></td>
<td>HDL</td>
<td>Yes</td>
<td>A 10 mg/dl change results in a 42% change in risk; most important risk factor except for age</td>
</tr>
<tr>
<td></td>
<td>LDL</td>
<td>No</td>
<td>A 20 mg/dl change results in a 6% change in risk</td>
</tr>
<tr>
<td>Rancho Bernardo</td>
<td>Cholesterol†</td>
<td>Yes</td>
<td>Women with (&gt;260) mg/dl have 2.5× increase in risk</td>
</tr>
<tr>
<td>Tecumseh</td>
<td>Cholesterol†</td>
<td>Yes</td>
<td>A 40 mg/dl change results in a 30% change in risk</td>
</tr>
<tr>
<td>Charleston</td>
<td>Cholesterol†</td>
<td>Yes/no</td>
<td>Only predictive in black women</td>
</tr>
<tr>
<td>Evans County</td>
<td>Cholesterol†</td>
<td>Yes/no</td>
<td>Only predictive in white women</td>
</tr>
<tr>
<td>Donolo-Tel Aviv</td>
<td>Cholesterol</td>
<td>Yes</td>
<td>Increased risk at (&gt;265) mg/dl and decreased risk at (&lt;200) mg/dl</td>
</tr>
<tr>
<td>Nurses Study</td>
<td>Cholesterol†</td>
<td>Yes</td>
<td>History of hypercholesterolemia increases risk 2×</td>
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<tr>
<td>Gothenburg</td>
<td>Cholesterol</td>
<td>No</td>
<td>Increased risk seen for myocardial infarction but not other end points</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein.

\*\(p<0.05\). †HDL and (or) LDL not assessed. Adapted from Bush.40 Used by permission.

above age categories are many times those of middle-aged adults. As indicated above, a substantial amount of CHD morbidity and mortality in the elderly is among women. Because of the high rate among older people, a small percentage shift in disease rates may translate into a large difference in the number of CHD deaths. For example, a 1% decline in CHD mortality in those aged 65 and above would result in over 4,200 fewer CHD deaths per year in the United States.

Several epidemiologic studies in the United States have shown that men's total serum cholesterol levels increase until they reach their late 50s41,42 and thereafter gradually decrease. The same pattern has been observed in aging women, with a few years' delay. The gradual decrease in total serum cholesterol levels may reflect lower levels of LDL, VLDL, and triglycerides in the very elderly.43-45 It may also reflect the earlier death of individuals with the highest total serum cholesterol levels.

Nevertheless, recent studies show that both total serum cholesterol and lipoprotein-cholesterol levels are predictive of disease in the elderly. For example, Framingham investigators reported that high LDL is associated with an increased risk of CHD at all ages through age 82,46 whereas HDL is negatively correlated with CHD risk for individuals aged 49–82.47 These findings complement a study showing that individuals in their 80s and 90s tend to have low levels of LDL and high levels of HDL.43

The most recent analysis of the Framingham data also indicates that total serum cholesterol is a coronary risk factor for the elderly.48 This latest analysis determined how much of an individual's risk of CHD could be attributed to certain coronary risk factors, including elevated serum cholesterol levels. The investigators found that although the relative risk of CHD due to elevated serum cholesterol levels declines with increased age, the attributable risk resulting from rises in cholesterol levels increases with age. Attributable risk is a better index than relative risk of the absolute public health risk (or benefit) resulting from a given risk factor. Simply put, an elevated serum cholesterol level contributes to more cases of CHD in older individuals than in younger ones.

These findings mirror the results of the Lipoprotein Cooperative Pooling Project in the late 1970s.49 The Pooling Project investigators noted that although the role of serum cholesterol in relative risk of CHD declined with age, attributable risk did not decline.

The NCEP and AHA guidelines point out that there is much room for clinical judgment in dealing with individual patients, particularly the elderly. The guidelines emphasize that a less aggressive approach to dietary restriction and especially to drug therapy is appropriate in elderly patients. Overall, however, the evidence supports the conclusion that reduction of high serum cholesterol levels in the elderly will reduce risk of CHD.

Are Cholesterol Interventions Cost-Effective?

The simplest form of cholesterol intervention is a low saturated fat, low-cholesterol diet. For most individuals, this diet is the only intervention necessary to lower serum cholesterol levels and reduce risk of CHD.50 The cost to the individual consumer of implementing this diet is minimal since low saturated fat, low-cholesterol foods such as fruits and vegetables are often less expensive than foods high in fat and cholesterol. In fact, one study showed that a diet with moderately low levels of saturated fat and dietary cholesterol would actually save the consumer $230 each year.51

Critics of the NCEP argue that the true cost of implementing cholesterol interventions is more than...
the cost to the individual consumer. They say the cost of visits to physicians, cholesterol tests, patient monitoring, lipid-modifying drug therapy, and treatment of side effects must also be counted. These costs, say the critics, can be enormous.

However, the critics disregard the fact that society has to compare the cost of cholesterol control with the cost of medical care for heart attacks and other CHD events and the economic cost to society resulting from the premature death of CHD victims. This perspective provides a more accurate measure of the cost and benefits of intervention.

Currently, approximately 1.5 million Americans suffer a heart attack each year, and approximately 300,000 coronary bypass surgeries are performed annually.52 The 5-year medical costs per case for treatment of acute myocardial infarction are estimated at $51,211; the estimated cost of coronary bypass surgery is $32,465.53 The AHA and the NHLBI estimate the costs of CHD to range from $41.5 billion52 to $56 billion (NHLBI, unpublished data, 1990) in 1990. The annual economic cost of all cardiovascular diseases is estimated at between $95 billion52 and $127 billion.54

As indicated above, a 10% reduction in serum cholesterol levels in the population, which should be possible by dietary modification alone, ought to result in a decrease in CHD rates of about 20%. This translates into an annual savings of at least $8–11 billion, which, in common sense terms, would effectively offset the $5–8 billion cost to the health care system (such as doctors' visits and laboratory costs) of a national cholesterol management effort with diet. The costs of cholesterol modification with medications would be larger, but the concomitant benefits of appropriate cholesterol interventions with medications would still more than offset the additional health care costs.53

Another way to assess the economic cost and benefits of a medical intervention program is the “cost per year of life saved” index. This approach is widely used by health care economists to determine cost-effectiveness of a prevention or treatment program. Analyses performed with this index have estimated the economic cost and benefits of cholesterol interventions by diet or drugs.52 (See Bibliography.) The cost per year of life saved varies considerably, depending on risk factor levels and each patient's personal characteristics. For persons with high absolute risk of CHD, such as men with risk factors in addition to high serum cholesterol, the cost per year of life saved is very small. Most importantly, however, the range of estimates of cost per year of life saved for cholesterol intervention are well within the range of a variety of widely used and accepted medical interventions. These include treatment of mild hypertension, estrogen replacement therapy, neonatal intensive care, breast cancer screening, coronary bypass surgery, and coronary care units. By this quantitative analysis, cholesterol intervention is at least as cost-effective as these accepted medical treatments.

Thus, whether measured by food bills and readily identified CHD costs or the more complicated cost per year of life saved formula, cholesterol interventions are cost-effective. It has been suggested that the NCEP may represent “one of the best bargains available to society for reducing pain, suffering and death from the nation's number one fatal disease.”53

Conclusion

This American Heart Association and National Heart, Lung, and Blood Institute joint statement has reviewed the evidence of the direct role of cholesterol in the development of atherosclerosis and CHD. Numerous epidemiologic and laboratory studies have confirmed the continuous, positive correlation of elevated serum cholesterol levels to increased CHD risk. Clinical studies have shown that modification of serum cholesterol by diet or drugs can lower that risk. The benefits of modifying serum cholesterol levels extend to men and women, young and old, those with high-risk LDL serum cholesterol levels, and those with borderline high-risk levels. Furthermore, cholesterol interventions are cost-effective. The evidence more than justifies the current national program for cholesterol modification.

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