Prevention of Coronary Heart Disease by Diet and Lifestyle

Evidence From Prospective Cross-Cultural, Cohort, and Intervention Studies

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Research on the cause of coronary heart disease has been ongoing for approximately a century.[1] From the beginning, diet played a prominent role in research on the origin of coronary heart disease. The original diet-heart hypothesis was very simple. Cholesterol is a constituent of the atherosclerotic plaque. Therefore, it was thought that there was a direct relation between cholesterol in the diet (ie, eggs), cholesterol in the blood, cholesterol in the plaque, and its clinical complications, such as myocardial infarction.

In the second part of the past century, it became clear that dietary cholesterol played a minor role in regulating serum cholesterol levels. It was also shown that dietary fatty acids are the major determinants of serum cholesterol.[2] The study of lipoprotein metabolism showed that the cholesterol-rich LDL fraction, not total cholesterol, was most strongly related to the development of atherosclerosis and its sequelae.[3] Experimental research was essential to understand the mechanisms by which genes, hormones, and diet interact to regulate the serum cholesterol level.[4] LDL cholesterol levels can be increased by saturated fatty acids, especially those with 12 to 16 carbon atoms, and by *trans* fatty acids.[5]

Several hypotheses have been proposed to explain the initiating events in atherogenesis, eg, the response-to-injury, response-to-retention, and oxidation hypotheses.[6–8] These hypotheses are not mutually exclusive and may even be compatible with each other. The oxidation hypothesis emphasizes the importance of oxidative modification in the atherosclerotic process, because compared with native LDL, oxidized LDL is preferentially taken up in the arterial wall.[8] This hypothesis makes a role of diet and lifestyle in atherogenesis likely, because LDL can be oxidized by smoking, for example, and oxidation can be prevented by dietary antioxidants, eg, vitamins and polyphenols.

There is overwhelming evidence that smoking, alcohol, and physical activity are important determinants of coronary heart disease. Prospective cohort studies showed a strong, graded relationship between cigarette smoking and coronary heart disease.[9] A moderate alcohol intake of 1 or 2 drinks per day is associated with a 30% to 40% lower risk of coronary heart disease.[10] Prospective cohort studies have also shown that the relative risk of coronary heart disease for inactive subjects compared with active persons is ≈2 times higher.[11]

Complex interactions between diet, lifestyle, and lipoprotein metabolism determine the development of atherosclerosis and its complications. This article reviews the evidence from major prospective cross-cultural, cohort, and intervention studies and focuses on the effects of a healthy diet and lifestyle on heart health. Recently, the results of large prospective cohort studies became available that show that a healthy diet and lifestyle, along with low levels of serum cholesterol and blood pressure and not smoking, are associated with a low risk of coronary heart disease.[12,13] The implications of these studies for primary and secondary prevention of coronary heart disease will be discussed.

Evidence From Cross-Cultural Studies

The interest in explaining differences in the occurrence of coronary heart disease between populations goes back almost a century. In 1916, the Dutch physician De Langen published an article titled "Cholesterol Metabolism and Racial Pathology."[14] He noted that the cholesterol levels of Dutch immigrants in the former Dutch Indies were approximately twice as high as those of native Javanese. He hypothesized that these differences were due to differences in diet and that hypercholesterolemia was associated with metabolic diseases such as atherosclerosis, diabetes, obesity, and nephritis. However, it took approximately half a century before the associations between diet, cholesterol, and coronary heart disease were studied in a systematic way.

In the 1950s, Keys and coworkers performed pilot studies in the United States, Japan, and northern and southern Europe which showed that cholesterol levels were high in the United States and Finland and low in Japan and southern Europe.[15] By visiting hospitals in these countries, they also noted large differences in the prevalence of coronary heart disease patients and observed substantial differences in dietary pat-

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terns. They hypothesized that cross-cultural differences in diet could be associated with differences in average population serum cholesterol levels and population rates of coronary heart disease mortality.

The Seven Countries Study began in 1958, and 12 763 men aged 40 to 59 years were examined for risk factors for coronary heart disease. These men formed 16 cohorts in 7 countries: the United States, Finland, the Netherlands, Italy, Greece, the former Yugoslavia, and Japan. In addition to a physical examination, information on biological risk factors (eg, serum cholesterol, blood pressure, and anthropometric measurements) was collected and an ECG was taken. In small random samples of each cohort, information on diet was collected by use of 7-day food records. The risk factor surveys were repeated after 5 and 10 years, and mortality data were collected up to 25 years. In that period, ≈6000 men died, and coronary heart disease was the underlying cause of death in 1500 men.

All dietary data were coded in a standardized way in 1986 and summarized in 16 major food groups.[16] Around 1960, the consumption of milk, potatoes, butter, and sugar products was very high in Finland. A similar but lower consumption pattern was observed in the Netherlands. Fruit, meat, and pastry consumption was high in the United States. Cereal and wine consumption was high in Italy, and bread consumption was high in the former Yugoslavia. In Greece, the consumption of olive oil and fruit was high, and the Japanese diet was characterized by a high consumption of fish, rice, and soy products. The average consumption of animal food groups, with the exception of fish, was positively associated with 25-year coronary heart disease mortality rates, and vegetable food groups showed an inverse association.[17]

Food composites were prepared that represented the average food intake of each cohort, and subsequently, different nutrients were determined in a central laboratory in 1987. In this way, information was obtained about population average intake of such things as fatty acids and antioxidants during the baseline survey.[18,19] The average population intake of saturated fat was strongly related to 10- and 25-year population coronary heart disease mortality rates.[18,20] Population average serum cholesterol was also significantly associated with 25-year population coronary heart disease mortality rates, although this correlation coefficient was weaker than that for saturated fat ($r=0.73$ versus $r=0.88$). This suggests that in addition to the effect of saturated fatty acids on serum cholesterol, they also have an effect on coronary heart disease independent of their effect on serum cholesterol. There is evidence that saturated fat influences indicators of thrombosis.[21]

Metabolic research has shown that modification of LDL is of utmost importance in the development of atherosclerosis and its complications. It is therefore hypothesized that not only is LDL cholesterol elevation by saturated fatty acids of importance in explaining population differences in coronary heart disease mortality, but smoking and dietary antioxidants could play a role. The Seven Countries Study showed that in addition to saturated fatty acids, the prevalence of smokers and population average intake levels of flavonols were independent contributors in explaining population differences in coronary heart disease mortality rates.[19] Flavonols are polyphenols with strong antioxidant properties that are present in tea, apples, onions, and red wine. The average population intake of (pro)vitamins with antioxidant properties, eg, vitamin E, β-carotene, and vitamin C, was not associated with long-term coronary heart disease mortality rates.[22]

Another international study that investigated cross-cultural relations between lifestyle factors (eg, smoking), biological risk factors (eg, serum cholesterol, blood pressure, and body mass index), and coronary heart disease is the World Health Organization MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) project.[23] In this project, the secular changes in major risk factors were analyzed in relation to secular changes in coronary heart disease attack rates across 38 populations of 21 countries, most of them European. In men aged 55 to 64 years, 10-year population changes in serum cholesterol level alone explained 35% of the variance of change in fatal and nonfatal coronary events. When smoking, body mass index, and systolic blood pressure were also taken into account, they together explained half of the population changes in coronary heart disease attack rates.[23] Results of the Seven Countries Study showed that in addition to baseline average serum cholesterol levels, changes in population average serum cholesterol levels during 10 years of follow-up were related to population coronary heart disease mortality rates.[24] It can be concluded that both the level of and changes in serum cholesterol and lifestyle factors contribute to coronary heart disease mortality rates in populations.

Cross-cultural evidence explains what happens at the population level. Evidence from large prospective cohort studies and controlled intervention trials is needed to determine the causal nature of associations between diet, lifestyle, and the onset of coronary heart disease in individuals as opposed to the occurrence of coronary heart disease in populations.

Evidence From Prospective Cohort Studies

For more than 50 years, prospective cohort studies, such as the Framingham Heart Study, have been performed. Such studies have identified serum cholesterol, blood pressure, and cigarette smoking as major risk factors for coronary heart disease. The relations between these risk factors and coronary heart disease are independent, strong, continuous, and graded. These studies suggested that the lower the risk factor profile, the lower the risk for coronary heart disease and all-cause mortality. However, very large cohort studies with long follow-up periods were needed to show the positive health effects of no smoking, low serum cholesterol levels ($<$5.17 mmol/L), and low blood pressure levels ($<$120/80 mm Hg).

Recently, results of 2 large prospective cohort studies, the Multiple Risk Factor Intervention Trial (MRFIT) and the Chicago Heart Association Detection Project in Industry (CHA), were published.[13] In total, risk factor data were available for ≈360 000 men aged 18 to 59 years and $>$6000 women aged 40 to 59 years. The participants in the MRFIT study were followed up for 16 years and those in the CHA

study for 22 years. The percentage of persons who did not smoke and had low serum cholesterol and blood pressure levels in these cohorts was low and varied between 4.8% and 9.9%. The age-adjusted relative risks of coronary heart disease mortality for low-risk persons compared with those who smoked and had elevated cholesterol and blood pressure levels varied between 0.08 in CHA men aged 18 to 39 years and 0.23 in CHA men aged 40 to 59 years. The life expectancy of persons at low risk was 9.5 years longer in CHA men aged 18 to 39 years and 5.8 years longer in CHA women aged 40 to 59 years compared with persons at elevated risk. These results illustrate the great impact of low risk factor levels on coronary heart disease risk and health in general.

The effect of a healthy diet and a healthy lifestyle on coronary heart disease could be tested in the Nurses Health Study, in which 84 129 women aged 30 to 55 years were enrolled and followed up for 14 years.[12] In that study, a healthy lifestyle was defined as no smoking, consuming at least half a drink of alcoholic beverage per day, engagement in moderate to vigorous physical activity for ≥30 minutes per day, and a body mass index <25 kg/m^2. A healthy diet was defined as the highest 40% of the cohort for the consumption of cereal fiber, marine n-3 polyunsaturated fatty acids, folate, and ratio of polyunsaturated to saturated fatty acids and low in *trans* fatty acids and glycemic load, which reflects the extent to which diet raises blood glucose levels. These lifestyle and dietary factors were related to 14-year coronary heart disease incidence.

The strongest association was observed for smoking and coronary heart disease (relative risk of 5.48, 95% CI 4.67 to 6.42) for nurses who smoked >12 cigarettes per day compared with never-smokers. For alcohol consumption, exercise, body mass index, and diet score, the risk ratios varied between 1.41 and 1.90. Women who did not smoke, exercised moderately to vigorously, drank >4 g of alcohol per day, and who had a body mass index <25 kg/m^2 and a diet score in the upper 2 quintiles had a risk ratio of 0.17 (95% CI 0.07 to 0.41) and a population attributable risk of 82% (95% CI 58% to 93%). A dose-response relation was also observed. When more low levels of risk factors were present, the effect on prevention of coronary heart disease was larger. In addition, in nonsmokers, a substantial effect was observed for the other lifestyle factors and diet. The 4% of nonsmoking nurses who also had low values for the other 4 risk factors had a risk ratio of 0.25 (95% CI 0.10 to 0.60) for coronary heart disease incidence compared with the other nonsmoking nurses.

The results of these large, prospective cohort studies show that persons with low levels of biological risk factors (eg, serum cholesterol and blood pressure) and persons who adhere to a healthy lifestyle and diet are at very low risk for coronary heart disease. This confirms the evidence from cross-cultural studies that population coronary heart disease mortality rates are largely determined by diet and smoking. However, evidence from clinical trials is needed to prove the causality of the role of dietary and lifestyle factors in the origin of coronary heart disease.

Evidence From Dietary and Lifestyle Intervention Studies

Comprehensive controlled trials investigating the combined effects of a healthy lifestyle and diet on disease end points in individuals are expensive and difficult to perform because of the difficulty in obtaining substantial differences in lifestyle and diet between the experimental and control groups. It is also almost impossible to avoid a carryover effect of a healthy lifestyle and diet advice from the experimental group to the control group. An example of a primary prevention trial that used an intervention with regard to more than 1 factor is the Oslo trial.[25] In this trial, intervention was focused on both diet and smoking. In secondary prevention, the most emphasis was given to either antismoking advice[26] or diet, either by serum cholesterol lowering[27] or by other dietary interventions.[28,29] There is, however, also a need to test the combined effect of different dietary and lifestyle changes on different health outcomes in cardiac patients.

In the Oslo trial, the effect of dietary and smoking advice was tested in 1232 healthy men aged 40 to 49 years. These men had high serum cholesterol levels (7.5 to 9.8 mmol/L), were mostly smokers (80%), had systolic blood pressures below 150 mm Hg, and were at very high risk for coronary heart disease.[25] They were randomized into 2 groups; the intervention group received dietary and antismoking advice, and the control group did not receive any advice. The advised diet was low in saturated fat and high in fiber. Saturated fat intake decreased from 18% to 8% of total energy intake, and saturated fat was partly replaced by n-6 polyunsaturated fatty acids. This resulted in a 13% difference in serum cholesterol between the experimental and control groups. This difference was in agreement with the difference in fatty acid composition of the diet between the 2 groups.[30] Besides the difference in diet, 25% of smokers in the experimental group stopped smoking compared with 17% in the control group. These differences were associated with a 47% difference in the sum of fatal and nonfatal myocardial infarction and sudden death between the 2 groups.

At the end of the Oslo trial, the average serum cholesterol level of the experimental group was still high (≈7 mmol/L). This is comparable to the population average of the eastern Finnish cohort at the beginning of the Seven Countries Study.[15,18] This cohort had the highest coronary heart disease mortality rate in the subsequent 25 years. The average serum cholesterol level of participants in the West of Scotland Coronary Prevention Study (WOSCOPS) at entry into the trial was also 7 mmol/L.[31] In that trial, pravastatin was used to lower serum cholesterol. Reduction of the average serum cholesterol level in that trial by 20% to 5.6 mmol/L was associated with a 31% reduction in coronary events. It may therefore be assumed that if the average serum cholesterol level at entry into the Oslo trial of 8.3 mmol/L was reduced to 5.6 mmol/L by a healthy diet, antismoking advice, and the use of a statin, there would have been a substantial reduction in major coronary events. This suggests that the occurrence of coronary heart disease can be strongly decreased by lowering serum cholesterol below 5.5 mmol/L and by not smoking.

In the first generation of primary and secondary prevention trials, serum cholesterol was lowered by replacing saturated

fat with linoleic acid, an n-6 polyunsaturated fatty acid. In 17 dietary intervention trials, an average reduction in serum cholesterol of ≈10% was obtained.[27] This was accompanied by nonsignificant reductions in major coronary events and all-cause mortality of 13% and 6%, respectively. The 5 primary and secondary prevention trials with the largest reduction in serum cholesterol (13% on average) showed a significant 30% reduction in major coronary events and an 11% reduction in all-cause mortality. These results suggest the larger the reduction in serum cholesterol, the larger the effect on coronary events and all-cause mortality.

Cholesterol lowering is not the only route through which diet can influence the occurrence of coronary heart disease in cardiac patients. Dietary changes that influence other metabolic pathways can also be beneficial.[28,29] The Diet And Reinfarction Trial (DART) trial showed a 32% reduction in coronary heart disease mortality and a 29% reduction in all-cause mortality because of consumption of oily fish at least twice a week.[28] An even more spectacular reduction in coronary and all-cause mortality of 65% and 56%, respectively, was obtained after 46 months of follow-up in the Lyon Diet Heart Study.[29] The intervention in that study consisted of a Mediterranean-type diet enriched with α-linolenic acid. There is an urgent need to replicate these trials under controlled conditions because of their potential importance for coronary heart disease prevention.[32,33]

For hypertensive patients, blood pressure lowering is very important because of their high risk for cardiovascular events. Drug trials showed an average reduction of diastolic blood pressure of 6 mm Hg in hypertensive persons.[34] A similar decrease was obtained by dietary intervention in the Dietary Approaches to Stop Hypertension (DASH) trial.[35] This decrease in blood pressure was achieved by a diet rich in fruits, vegetables, and dairy products with a low saturated fat content. Such a diet is low in saturated fat and high in potassium, calcium, and magnesium. This trial provided the first experimental evidence that in addition to sodium, potassium, calcium, and magnesium are important dietary determinants of blood pressure, as was suggested by the results of epidemiological studies.[36,37] The recently published results of the second DASH trial, in which sodium intake was lowered and intake of potassium, calcium, and magnesium was increased, showed that the combined effect of sodium reduction and the DASH diet was greater than their single effects.[38] These results suggest that a healthy diet should also be an integral part of hypertension treatment.

For cardiac patients, it is also very important to stop smoking. A study showed that if 36% of cardiac patients stop cigarette smoking, it results in a 30% reduction in cardiovascular mortality.[26] Lack of exercise is also an important risk factor for coronary and all-cause mortality. However, reliable trials on the health effects of exercise in cardiac patients have not been performed.[32]

Large comprehensive controlled trials on dietary and lifestyle interventions in cardiac patients that examine the effects on coronary and all-cause mortality have not been performed. A small trial has been done in 48 patients using quantitative coronary arteriography as an end point.[39] The intervention consisted of intensive dietary and lifestyle changes, eg, a low-fat, whole-food vegetarian diet with 10% of energy from fat; aerobic exercise; stress management training; smoking cessation; and group social support. After 5 years of follow-up, a relative improvement in diameter stenosis of 7.9% was observed compared with a 27.7% worsening in the control group ($P=0.001$). The risk ratio for a cardiac event in the control group compared with the experimental group was 2.47 (95% CI 1.48 to 4.20).

These results provide evidence that healthy eating lowers the risk for coronary heart disease both in free-living high-risk persons and in cardiac patients. There is, however, a need to test what the most effective dietary interventions are.[40] The combined effect of a healthy diet and lifestyle factors is larger than their independent effects. Side effects of interventions in diet and lifestyle are unknown. There is a need to test the combined effect of the most effective dietary and lifestyle interventions in primary and secondary prevention and to monitor their effects on health in general in order to trace possible unforeseen negative consequences.

Implications for Primary and Secondary Prevention of Coronary Heart Disease

This overview shows that the evidence regarding diet and lifestyle factors in relation to the occurrence of coronary heart disease is congruent. Prospective cross-cultural, cohort, and intervention studies showed that diet and smoking are major determinants of coronary heart disease occurrence. In addition to dietary factors and smoking, alcohol and physical activity are important determinants of the individual risk for coronary heart disease.[10,41] The observational evidence about these risk factors is very strong and consistent. Metabolic explanations (eg, effects on lipid metabolism and the thrombotic process) are also available to explain the protective effect of moderate alcohol consumption and moderate to vigorous exercise on coronary heart disease. However, reliable trials examining the impact of these risk factors on coronary and all-cause mortality have not been performed.

It has been thought for a long time that dietary and lifestyle interventions are only of importance for primary prevention. However, the results of primary prevention trials in high-risk persons and secondary prevention trials in cardiac patients both showed that substantial reductions in the risk for coronary heart disease can be obtained by dietary and lifestyle changes.[25,29,39] It has also been shown that serum cholesterol and blood pressure are related to risk of coronary heart disease both in persons free of coronary heart disease and in coronary patients.[42,43] One of the differences between cardiac patients and persons free of coronary disease is that the absolute risk of cardiac patients is substantially higher than for persons free of coronary disease, but the predictive power of risk factors is similar in the 2 groups.[42,43]

There is a great need to optimize dietary and lifestyle factors in high-risk persons and in cardiac patients. However, it is not easy to follow a healthy diet and lifestyle, even for cardiac patients, as can be shown by the results of the EUROASPIRE (European Action on Secondary Prevention by Intervention to Reduce Events) I and II surveys.[44] In 1995 to 1996 and 1999 to 2000, ≈3500 cardiac patients from 9 European countries were interviewed. During this 4-year

period, the prevalence of smokers among cardiac patients increased from 19% to 21%. The prevalence of obesity increased from 25% to 33%, and the prevalence of reported diabetes increased from 18% to 22%. These increases occurred despite frequently given advice on a healthy lifestyle and diet. One of the reasons for these disappointing results could be lack of a clear and simple message on what the most important lifestyle and dietary recommendations are in relation to low coronary risk.

In accordance with the task force report of the European Society of Cardiology on "Prevention of Coronary Heart Disease in Clinical Practice,"[45] the dietary guidelines of the American Heart Association,[46] the National Cholesterol Education Program,[47] and the conclusions reached from international comparisons of mortality,[48] the most important recommendations for lifestyle factors in relation to potential health gains are as follows:

- Don't smoke.
- If you use alcohol, do so in moderation.
- Be moderately to vigorously physically active (eg, brisk walking, biking, or gardening) at least 30 minutes each day.

The most important dietary recommendations are as follows:

- Keep an energy balance, indicated by a body mass index below 25 kg/m^2.
- Consume <10% of energy from saturated fat.
- Consume <2% of energy from *trans* fat.
- Eat (fatty) fish at least once a week.
- Eat ≥400 g of vegetables and fruits per day.
- Limit salt consumption to <6 g/d.

If these recommendations are followed, coronary heart disease can be eliminated to a large extent in the population aged <70 years, and by implementing these recommendations at middle-age, there will be lower annual costs for medical care in older age.[49]

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