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Diets to Prevent Coronary Heart Disease 1957-2013: What Have We Learned?

James E. Dalen, MD, MPH,[a] Stephen Devries, MD, FACC[b,c]

[a]Weil Foundation and University of Arizona College of Medicine, Tucson, Ariz; [b]Gaples Institute for Integrative Cardiology, Deerfield, Ill; [c]Division of Cardiology, Northwestern University, Chicago, Ill.

ABSTRACT

Our understanding of the potential cardioprotective properties of nutrition is relatively recent, with most relevant studies completed in the last several decades. During that time, there has been an evolution in the focus of nutritional intervention. Early trials emphasized reduction of dietary fat with the goal of preventing heart disease by reducing serum cholesterol. Results from trials focused exclusively on dietary fat reduction were disappointing, prompting subsequent studies incorporating a whole diet approach with a nuanced recommendation for fat intake. The Mediterranean-style diet, with a focus on vegetables, fruit, fish, whole grains, and olive oil, has proven to reduce cardiovascular events to a degree greater than low-fat diets and equal to or greater than the benefit observed in statin trials.

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One of the earliest clues that coronary heart disease is influenced by nutrition was the observation of Ignatowski in 1908[1] that high dietary intake of cholesterol promoted atherosclerosis in rabbits. Finking and Hanke[2] reported on Anitschkow's finding that a cholesterol-enriched diet led to fatty streaks and advanced atheromatous plaques in rabbits, similar to the lesions in patients with coronary atherosclerosis. Later, cholesterol was isolated from the atheromatous plaque of patients with coronary heart disease.[3]

In 1952, Kinsell[4] reported that replacement of animal fats with vegetable oil resulted in a dramatic decrease of serum cholesterol in patients. Groen et al[5] found that vegetarian diets were associated with reduction of cholesterol levels.

THE DIET HEART HYPOTHESIS

In 1957, Ancel Keys[6] cited extensive epidemiologic evidence suggesting that indigenous diets have an important impact on the variability of coronary heart disease across populations. It was well established that patients with coronary heart disease tend to have higher serum cholesterol levels than their clinically healthy counterparts. Those observations were pivotal for the development of the cholesterol hypothesis: Dietary saturated fat increases serum cholesterol, which in turn leads to coronary atherosclerosis.[6]

Keys et al[7] launched the Seven Countries Study in 1957. This cross-cultural prospective study of myocardial infarction and stroke in more than 12,000 middle-aged men in 16 cohorts in 7 countries added further support to the cholesterol hypothesis. They found that the intake of saturated fat varied considerably by region. Populations with the greatest intake of saturated fat were found to have the highest serum cholesterol levels. Follow-up studies confirmed that these groups also had the highest incidence of coronary heart disease.[7]

The link from dietary saturated fat to serum cholesterol levels to coronary heart disease seemed clear. The findings of the Seven Countries Study stimulated further inquiry to determine whether altering the diet could decrease serum cholesterol levels and, thereby, decrease the incidence of coronary heart disease.[8-12]

AMERICAN HEART ASSOCIATION DIETARY RECOMMENDATIONS

One of the first organizations to advocate dietary changes to decrease atherosclerosis was the American Heart Association (AHA). In 1957, the AHA Nutrition Committee, in

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Requests for reprints should be addressed to James E. Dalen, MD, MPH, 5305 Via Velazquez, Tucson, AZ 85750.

E-mail address: jdalenmd@gmail.com

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cooperation with the Society for the Study of Arteriosclerosis, published their recommendations in *The Journal of the American Medical Association.*[13] They concluded that "diet may play an important role in the pathogenesis of atherosclerosis and the fat content and the total calories in the diet are probably important factors. The type of fat, rather than the total or the ratio or balance between the saturated and certain unsaturated fats may be the determinant."

LOW-FAT DIETS

The 1957 AHA Nutrition Committee recommendations called for obese individuals to limit caloric intake by reducing dietary fat intake. "Diets containing 25% to 30% of calories from fat, rather than the current 40% to 45% can still provide palatable meals for our accustomed tastes."[13] This was the first suggestion that treating obesity with a low-fat diet might prevent coronary heart disease.

CLINICAL SIGNIFICANCE

- Diets to prevent cardiovascular disease have been advised for more than 50 years.
- Most diets have recommended decreasing saturated fats and dietary cholesterol and increasing polyunsaturated fats. These diets do decrease cholesterol levels, but they have not decreased cardiovascular disease.
- A newer approach is to increase and decrease certain food groups. This new approach has proven to be successful in preventing cardiovascular disease in primary and secondary prevention trials.

FROM LOW-FAT DIETS TO LOW SATURATED FAT/ INCREASED POLYUNSATURATED DIETS

In 1958, Brown and Page[14] noted that serum cholesterol levels may be treated by 2 dietary approaches: a strict low-fat diet and a diet containing a minimum of animal fat along with an increase in vegetable oil. By 1961, the recommendation of the AHA's Ad Hoc Committee on Dietary Fat and Atherosclerosis was more specific, "the reduction or control of fat consumption under medical supervision, with reasonable substitution of poly-unsaturated for saturated fats is recommended as a possible means of preventing atherosclerosis and decreasing the risks of heart attacks and strokes."[15] The focus then shifted from a low-fat diet to the substitution of polyunsaturated vegetable oil for saturated fat.

REDUCTION OF DIETARY CHOLESTEROL

In 1972, a joint statement from the National Academy of Sciences-National Research Council and the Council on Foods and Nutrition of the American Medical Association reported that the risk of coronary heart disease was linked to the blood cholesterol level.[16] They concurred with the AHA recommendation that cholesterol reduction can be most efficiently achieved by partial replacement of saturated with polyunsaturated fats, as well as a reduction in foods rich in cholesterol.[16]

CLINICAL TRIALS FOR SECONDARY PREVENTION OF CORONARY HEART DISEASE, 1957-1978

The US National Diet-Heart Study demonstrated that a low saturated fat, low dietary cholesterol diet could decrease serum cholesterol by 11% to 12% in a free-living population.[17]

REGRESSION OF CORONARY DISEASE THROUGH DIET AND LIFESTYLE INTERVENTION

In 1990, Ornish et al[18] reported a study of 48 patients with angiographically documented coronary heart disease. Twenty-eight patients followed a low-fat vegetarian diet that contained approximately 10% of calories as fat and 5 mg or less cholesterol per day. They also performed stress management (1 hour per day) and followed a program of moderate exercise (3 hours per week). Follow-up quantitative coronary angiography was performed after intervention and compared with angiograms in 20 control patients with documented coronary atherosclerosis. In the experimental group, 82% had an average change toward regression. There was angiographic evidence of progression in 53% in the control group.[18]

Coronary arteriography was repeated 5 years later. Additional regression was noted in 20 patients who maintained their lifestyle changes, with further progression in the 15 control patients.[19] As noted, these patients followed a very low-fat (10%) vegetarian diet.

AMERICAN HEART ASSOCIATION DIET RECOMMENDATIONS

Despite recommendations to restrict fat intake to less than 30% of daily calories, saturated fat to less than 10%, and cholesterol to less than 300 mg per day, these goals were not achieved by the US population. As noted in **Table 1**, the fat intake of the US diet was nearly the same in 2000[20] as in 1963.[21] American diets continue to include 30% or more calories from fat and more than 10% calories from saturated fat. Daily cholesterol consumption exceeded 300 mg/d in 1963, 1975, and 2000.

AN UNSUCCESSFUL PRIMARY PREVENTION TRIAL: THE MULTIPLE RISK FACTOR INTERVENTION TRIAL 1974-1982

In the Multiple Risk Factor Intervention Trial, a US multicenter clinical trial, more than 360,000 men aged 35 to 57 years were screened for blood pressure, cholesterol levels, and smoking. A total of 12,886 men in the top 15% of coronary heart disease risk by Framingham data were randomized to special intervention or usual care by their primary care physicians.[29] In the special intervention group,

Table 1 American Heart Association Dietary Guidelines Versus Actual US Diet

	Total Fat, %	Saturated Fat, %	Cholesterol (mg/d)	Reference
1957 AHA	25-30			13
1961 US	40-45			13
1961 AHA	25-35			15
1963 US	40.4	15.6	533	21
1968 AHA	30-35	10-12	<300	29
1969 US	39	15	530	21
1975 US	38.3	14.0	451	21
1982 AHA	<30	<10	<300	22
1993 AHA	<30	<10	<300	23
1993 US	37%	14%		24
1996 AHA	<30	<10	<300	25
2000 US	33	11%	341	20
2000 AHA	<30	<10	<300	26
2006 AHA	25-35	<7	<300	27
2011 AHA	<30	<7	<300	28

AHA = American Heart Association.

hypertension was treated with standard medications, and smoking cessation was promoted in group and individual counseling sessions.

The dietary goals for those randomized to special intervention were to reduce saturated fat to less than 10% caloric intake and cholesterol to less than 300 mg/d, with increased polyunsaturated fat (>10%). The goals were changed in 1976 to less than 8% saturated fat and less than 250 mg of dietary cholesterol per day.[29]

The 3 dietary goals were nearly accomplished (**Table 2**). Saturated fat intake decreased from 14.2% of calories to 10.5% (goal was <8%). Daily cholesterol intake decreased from 451 mg/d to 269 mg/d (goal was <250 mg). Polyunsaturated fats increased from 6.4% to 8.4% (goal was >10%).[30]

Despite the significant reduction in dietary fat, the changes in total cholesterol and low-density lipoprotein cholesterol after 7 years of intervention were modest. Total cholesterol decreased by 5% in those receiving special care and 2.9% in those receiving community care.[29]

The end points of reduction in total mortality and coronary death were not achieved, as shown in **Table 3**. This lack of efficacy was striking given that hypertension was better controlled and cigarette cessation was more successful in the special intervention group.

Table 2 Diet at End of the Multiple Risk Factor Intervention Trial[29]

	Community	Special Intervention
Total fat, %	38.1	34.1
Saturated fat, %	13.7	10.5
MUFA, %	14.9	12.7
PUFA, %	6.7	8.4
Cholesterol, mg/d	414	269

MUFA = monounsaturated fatty acid; PUFA = polyunsaturated fatty acid.

Table 3 End Points of the Multiple Risk Factor Intervention Trial[29]

	Special Care	Controls	*P*
CV death	17.5%	19.2%	NS
All-cause deaths	32.8%	34%	NS
Stroke	4.9%	4.2%	NS

CV = cardiovascular; NS = not significant.

EARLY TRIALS OF DIETARY APPROACHES TO SECONDARY PREVENTION

The Diet Reinfarction Trial: 1986-1989

In 1989, Burr et al[31] reported the results of the Diet Reinfarction Trial, a randomized controlled trial of 2033 men aimed at the secondary prevention of myocardial infarction. Participants were randomized to receive advice on 3 dietary factors: (1) total fat intake and the ratio of polyunsaturated to saturated fat; (2) fatty fish consumption; and (3) cereal fiber intake. There was a slight (3.6%) reduction in cholesterol in those advised to decrease fat. There was no decrease in cholesterol in those advised to increase fatty fish or cereal intake. None of these 3 factors influenced the 2-year incidence of reinfarction or cardiac death. However, those counseled to eat fatty fish had a 29% reduction in 2-year all-cause mortality.[31]

Indian Experiment of Infarct Survival (1989-1992)

In the Indian Experiment of Infarct Survival study,[32] 406 patients with suspected acute myocardial infarction were randomized to 1 of 2 low-fat diets. The experimental group was counseled on a "whole diet approach" that included increased intake of fruits, vegetables, nuts, and fish. Total fat was reduced to 24% of daily calories in the experimental group and 28% in controls ($P < .001$). Saturated fat was reduced in the experimental group (7.2% vs 10.8%, $P < .001$). Dietary cholesterol was 147 mg/d in the experimental group compared with 287 mg/d in the control diet.

The experimental group lowered total cholesterol by 13% compared with 5% in the control diet. There was a striking reduction in the combination of nonfatal myocardial infarction, fatal myocardial infarction, and sudden death from 82 patients assigned to the control diet to 50 patients on the experimental diet ($P < .001$)[32]

The Lyon Diet Heart Study 1988-1997

In the Lyon Diet Heart Study, 605 survivors of a first myocardial infarction were randomized to a Mediterranean-style diet or a "prudent" low-fat diet.[33] The Mediterranean-style diet, a whole diet approach, is low in animal products

Table 4 Daily Nutrient Intake at the End of the Lyon Diet Heart Study[34]

	Mediterranean Diet	Control	*P* Value
Total fat, % total calories	30.4	33.6	.002
Saturated fatty acids, %	8.0	11.7	.0001
Monounsaturated FA, %	12.9	10.3	.0001
Polyunsaturated FA, %	4.6	6.1	.0001
Cholesterol, mg/d	203	312	.0001
Omega 3, %	0.84	0.29	.0001
Omega 6, %	3.6	5.3.	.001

FA = fatty acid.

and saturated fat, with an emphasis on the use of olive oil. It is rich in legumes, fruit, vegetables, and fish. Butter and cream were replaced with a canola-based margarine high in alpha-linolenic acid, an omega-3 fatty acid. Compared with controls, those randomized to the Mediterranean diet consumed significantly more bread, fruits, and margarine and less delicatessen foods, meats, butter, and cream.

As shown in **Table 4**, at the end of the trial, the percentage of daily calories from fat was 30.4% in the Mediterranean diet group and 33.6% in the low-fat/low-cholesterol control group ($P = .002$).[34] The calories derived from saturated fat also were lower in the Mediterranean diet group (8.0% vs 11.7%, $P = .0001$), as was the daily cholesterol intake (203 vs 312 mg/d mg, $P = .0001$). In addition, omega-3 consumption (from vegetables, fish, and margarine) was considerably higher and omega-6 consumption was lower for those on the Mediterranean diet.[34] At the end of the trial, there was no significant difference between the total serum cholesterol or low-density lipoprotein cholesterol levels in those on the 2 diets.[34]

The end points of the Lyon Diet Heart Study were cardiovascular death or nonfatal myocardial infarction. The trial was stopped after 27 months when an intermediate analysis showed that those on the Mediterranean diet had a 73% reduction in cardiovascular disease deaths and nonfatal myocardial infarction.[33] After 46 months, there were 44 cardiac deaths or nonfatal myocardial infarcts in the control group compared with 14 in those following the Mediterranean diet, a 72% reduction ($P < .0001$).[34]

21st Century Dietary Approach to Primary Prevention: The PREvención con DIeta MEDiterránean Study 2003-2012

The PREvención con DIeta MEDiterránean (PREDIMED) study evaluated 7447 men and women in Spain at increased risk of cardiovascular disease because of type 2 diabetes or 3 or more cardiac risk factors, but without evidence of cardiovascular disease. Participants were randomized to 1 of 3 diets: a Mediterranean-style diet supplemented with additional extra virgin olive oil, a Mediterranean-style diet supplemented with mixed nuts, or a control group that was counseled to follow a low-fat diet.[35]

Total fat intake was not restricted in those on the Mediterranean diet, but the source was predominantly from fatty fish and plant-based sources. Those randomized to the low-fat diet were advised to reduce all types of fat, including olive oil and nuts. Adherence to the low-fat diet was poor, and so their intake more closely resembled their baseline diet. A summary of dietary intake at the completion of the approximately 5-year trial is shown in **Table 5**. Total dietary fat was higher in the Mediterranean diet groups. Saturated fat and dietary cholesterol intake were similar in both groups.

The primary end point, a combination of stroke, myocardial infarction, and cardiovascular deaths, was reduced by 30% in the group randomized to a Mediterranean diet supplemented with extra virgin olive oil and 28% lower in the Mediterranean diet with mixed nuts compared with controls. Analysis of the primary end point revealed that most of the observed benefit was accounted for by a reduction in strokes.

Why Did the Multiple Risk Factor Intervention Trial Fail and PREvención con DIeta MEDiterránean Succeed?

Two primary prevention trials, 1 in the United States (1974-1982)[29] and 1 in Spain (2003-2012),[35] studied individuals at increased risk of cardiovascular disease but with no evidence of cardiovascular disease: The dietary goals in the Multiple Risk Factor Intervention Trial (MRFIT) focused on reducing cholesterol levels by limiting saturated fat and dietary cholesterol, and the PREDIMED study used a

Table 5 Daily Diet at the End of PREvención con DIeta MEDiterránean Trial[35] and Multiple Risk Factor Intervention Trial[30]

	Mediterranean + Olive	Mediterranean + Nuts	Low Fat	MRFIT
Total fat, %	41.2	41.5	37.0	34.1
Saturated fat, %	9.4	9.3	9.1	10.5
Cholesterol, mg/d	339	338	324	269
Monounsaturated fat, %	22.1	20.9	18.8	12.7
Polyunsaturated fat, %	6.1	7.7	5.5	8.4
Linoleic acid, g/d	12.2	16.0	10.0	NA
Alpha-linolenic, g/d	1.3	1.9	1.1	NA
Murine n-3, g/d	0.9	0.8	0.7	NA

MRFIT = Multiple Risk Factor Intervention Trial; NA = not available.

Table 6 Food Groups Shown to Decrease Risk of Coronary Heart Disease in Prospective Studies

Nuts[35-38]
Fruits[36-43]
Vegetables[36-42]
Green leafy vegetables[36,40,42]
Legumes[32,37,43]
Whole grain[36,38,43]
Fish[31,36,38,43]
Moderate alcohol[36,38]
Fiber[38,39]
Poultry[43]
Olive oil[35]

"whole diet approach" focused on specific food groups rather than individual dietary nutrients.

At the end of the trials, the MRFIT participants were consuming less fat and less dietary cholesterol than the 2 Mediterranean diet groups (olive oil and mixed nuts) in the PREDIMED study. Multiple prior trials[8-12] have shown that limiting total fat and dietary cholesterol is effective at lowering serum cholesterol but does not prevent myocardial infarction or cardiovascular death. In the MRFIT, 10.5% of calories were derived from saturated fat, somewhat higher than with the Mediterranean diet (9.4% and 9.3%).

The most striking difference was in the percentage of calories from monounsaturated fats: 12.7% in the MRFIT and 22.1% and 20.9% in the PREDIMED study. The strikingly favorable results of the Mediterranean diet studies are consistent with cardioprotective properties of its major constituents, as documented in prospective studies shown in **Table 6**.

DIET AND MORTALITY AMONG SURVIVORS OF MYOCARDIAL INFARCTION

Li et al[44] followed the course of 2258 women from the Nurses' Health Study and 1840 men from the Health Professionals Follow-up Study who survived an initial myocardial infarction. They used the Alternative Healthy Eating Index 2010 to assess their diet quality before and after their myocardial infarction. The index measures the intake of food items that are associated with lower chronic disease risk. The post-myocardial infarction Alternative Healthy Eating Index 2010 score was inversely associated with all-cause mortality (hazard ratio, 0.76; 95% confidence interval, 0.60-0.96; $P = .02$ for trend). The hazard ratio for cardiovascular mortality was 0.73 (95% confidence interval, 0.51-1.04; $P = .08$).

WHAT HAVE WE LEARNED?

Nearly all clinical trials in the 1960s, 1970s, and 1980s compared usual diets with those characterized by low total fat, low saturated fat, low dietary cholesterol, and increased polyunsaturated fats. Free-living volunteers were able to adhere to these diets whose goal was to decrease serum cholesterol to prevent cardiovascular events. These diets did reduce cholesterol levels. However, they did not reduce the incidence of myocardial infarction or coronary heart disease deaths.

On the basis of the results of the Diet Reinfarction Study,[31] the Lyon Diet Heart Study in 1994[33] and 1999,[34] the PREDIMED study in 2013,[35] and the recent report by Li et al,[44] it is clear that dietary patterns consistent with the traditional Mediterranean-style diet are particularly cardioprotective. Mediterranean-style diets are effective in preventing coronary heart disease even though they do not decrease total serum cholesterol or low-density lipoprotein cholesterol.[34]

CONCLUSIONS

The last 50 years of epidemiology and clinical trials have established a clear link among diet, atherosclerosis, and cardiovascular events. Nutritional interventions have proven that a "whole diet" approach with equal attention to what is consumed and what is excluded is more effective in preventing cardiovascular disease than low-fat, low-cholesterol diets.

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