

EFFECTS OF DIET AND EXERCISE IN MEN AND POSTMENOPAUSAL WOMEN WITH LOW LEVELS OF HDL CHOLESTEROL AND HIGH LEVELS OF LDL CHOLESTEROL

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ABSTRACT

Background Guidelines established by the National Cholesterol Education Program (NCEP) promote exercise and weight loss for the treatment of abnormal lipoprotein levels. Little is known, however, about the effects of exercise or the NCEP diet, which is moderately low in fat and cholesterol, in persons with lipoprotein levels that place them at high risk for coronary heart disease.

Methods We studied plasma lipoprotein levels in 180 postmenopausal women, 45 through 64 years of age, and 197 men, 30 through 64 years of age, who had low high-density lipoprotein (HDL) cholesterol levels (≤ 59 mg per deciliter in women and ≤ 44 mg per deciliter in men) and moderately elevated levels of low-density lipoprotein (LDL) cholesterol (>125 mg per deciliter but <210 mg per deciliter in women and >125 mg per deciliter but <190 mg per deciliter in men). The subjects were randomly assigned to aerobic exercise, the NCEP Step 2 diet, or diet plus exercise, or to a control group, which received no intervention.

Results Dietary intake of fat and cholesterol decreased during the one-year study ($P<0.001$), as did body weight, in women and men in either the diet group or the diet-plus-exercise group, as compared with the controls ($P<0.001$) and the exercise group ($P<0.05$), in which dietary intake and body weight were unchanged. Changes in HDL cholesterol and triglyceride levels and the ratio of total to HDL cholesterol did not differ significantly among the treatment groups, for subjects of either sex. The serum level of LDL cholesterol was significantly reduced among women (a decrease of 14.5 ± 22.2 mg per deciliter) and men (a decrease of 20.0 ± 17.3 mg per deciliter) in the diet-plus-exercise group, as compared with the control group (women had a decrease of 2.5 ± 16.6 mg per deciliter, $P<0.05$; men had a decrease of 4.6 ± 21.1 mg per deciliter, $P<0.001$). The reduction in LDL cholesterol in men in the diet-plus-exercise group was also significant as compared with that among the men in the exercise group (3.6 ± 18.8 mg per deciliter, $P<0.001$). In contrast, changes in LDL cholesterol levels were not significant among the women (a decrease of 7.3 ± 18.9 mg per deciliter) or the men (10.8 ± 18.8 mg per deciliter) in the diet group, as compared with the controls.

Conclusions The NCEP Step 2 diet failed to lower LDL cholesterol levels in men or women with high-risk lipoprotein levels who did not engage in aerobic exercise. This finding highlights the importance of physical activity in the treatment of elevated LDL cholesterol levels. (N Engl J Med 1998;339:12-20.)

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ELEVATED serum levels of low-density lipoprotein (LDL) cholesterol and reduced levels of high-density lipoprotein (HDL) cholesterol are important independent risk factors for coronary heart disease.^{1,2} Reducing LDL cholesterol levels by means of drug therapy has been shown to reduce the incidence of coronary heart disease among men with hypercholesterolemia and dyslipidemia^{3,4} and also to reduce the rate of death due to coronary heart disease in patients with the disease.⁵ It is believed that reductions in the serum LDL cholesterol level produced by dietary therapy will have similar benefits⁶; however, the diet recommended for reducing LDL cholesterol levels may reduce HDL cholesterol levels to a similar degree.^{7,8}

Earlier, we demonstrated that weight loss increased HDL cholesterol levels in moderately overweight men⁹ and that physical activity prevented the lowering of HDL cholesterol levels that usually results from a low-fat diet in overweight men and women.¹⁰ Subsequently, the guidelines of the National Cholesterol Education Program (NCEP) Adult Treatment Panel, emphasizing the incorporation of weight loss and physical activity into dietary therapy for cholesterol management, were published.¹¹

In the present one-year, randomized, controlled study of men and postmenopausal women with low HDL cholesterol levels and elevated LDL cholesterol levels (the Diet and Exercise for Elevated Risk trial), we examined the effects of changes in diet and exercise, alone and together, on plasma lipoproteins. We hypothesized that HDL cholesterol levels would be raised by exercise but lowered by the NCEP Step 2 diet, that LDL cholesterol levels would be reduced by the diet, and that the ratio of LDL to HDL cholesterol would be most improved by combining the diet with regular exercise.

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METHODS

Design of the Study

We used several strategies to recruit postmenopausal women 45 through 64 years of age and men 30 through 64 years of age, who had both plasma HDL cholesterol levels below 60 mg per deciliter (1.55 mmol per liter) for women and 45 mg per deciliter (1.14 mmol per liter) for men, the approximate mean for the U.S. population,¹² and plasma LDL cholesterol levels greater than 125 mg per deciliter (3.23 mmol per liter) but below 210 mg per deciliter (5.43 mmol per liter) for women and greater than 125 mg per deciliter but below 190 mg per deciliter (4.91 mmol per liter) for men. Potential subjects were excluded if they reported a history of heart disease, stroke, diabetes, recent cancer, other life-threatening illness, or any condition that limited their ability to engage in moderate-intensity exercise; if they were currently using insulin or medications for heart problems, blood pressure, or high serum cholesterol levels; or if they smoked more than nine cigarettes per day or consumed more than four alcoholic drinks daily. The women who enrolled in the study agreed not to change their hormonal therapy, if any, for one year. After providing informed consent, participants had to meet criteria for fasting plasma HDL and LDL cholesterol levels, triglyceride levels (≤ 500 mg per deciliter [5.64 mmol per liter]), and resting blood pressure ($< 160/95$ mm Hg) at each of two morning clinic visits. Additional criteria included plasma glucose levels that were less than 140 mg per deciliter (7.77 mmol per liter) while the subjects were fasting and less than 200 mg per deciliter (11.10 mmol per liter) after an oral glucose load; a body-mass index (the weight in kilograms divided by the square of the height in meters) of 32 or less for women and 34 or less for men; and normal results on a maximal treadmill exercise test.

After the base-line assessments, 180 women and 197 men were randomly assigned to one of four groups: that assigned to follow the NCEP Step 2 diet (47 women and 49 men); that assigned to aerobic exercise only (44 women and 50 men); that assigned to both the NCEP Step 2 diet and exercise (43 women and 51 men); or a control group, which received neither intervention (46 women and 47 men). Assignments were made by computer with use of a modified Efron procedure,¹³ which weighted the probability of assignment in order to balance groups in terms of sample size and average HDL cholesterol levels and LDL cholesterol levels.

Dietary recommendations, based on the goals of the NCEP Step 2 diet (less than 30 percent total fat, less than 7 percent saturated fat, and less than 200 mg of cholesterol per day),¹¹ were presented to the subjects by registered dietitians. Participants entered a 12-week adoption phase in which an individualized counseling session was followed by eight one-hour, mixed-sex group lessons on replacing dietary sources of saturated fat with complex carbohydrates, low-fat dairy foods, and other alternatives, including lean meats. Weight loss was not emphasized in the group sessions, which were held separately for the diet-alone and diet-plus-exercise groups and which averaged 15 persons per group. A six-to-eight-month maintenance phase consisted of monthly contacts with study dietitians, by mail or telephone or in group or private meetings.

The aerobic-exercise program began with a private meeting with members of the exercise staff, followed by a six-week adoption phase in which participants attended supervised, one-hour, mixed-sex exercise sessions, three times per week, that were held separately for the exercise-alone and diet-plus-exercise groups. The subjects were instructed not to discuss diet during these sessions. Throughout a seven-to-eight-month maintenance phase, participants could attend supervised group sessions three times per week, supplement the required monthly group sessions with home-based activities, or both, with the goal of engaging in aerobic activity equivalent to at least 16 km (10 mi) of brisk walking or jogging each week. The controls were asked to maintain their usual diet and exercise habits until the tests at one year of follow-up were completed.

Clinical Procedures

At base line and after one year, subjects came to the clinic several times to provide data on physical measures, aerobic fitness, and plasma lipoprotein and glucose levels. The body-mass index was determined by measuring the weight on a standard beam balance, during two visits, and the height with a Harpenden stadiometer. The means of three measures of the following were recorded with participants standing: waist (narrowest circumference viewed from the front); abdominal girth (at the umbilicus); and hip (largest horizontal circumference around the buttocks). Resting heart rate and systolic and diastolic blood pressure were determined in duplicate on two morning visits, as previously described.¹⁴ Oxygen uptake during a graded treadmill exercise test was determined every 30 seconds, with use of a previously described semiautomated metabolic-analysis system.¹⁵ For aerobic capacity (maximal oxygen uptake in milliliters of oxygen consumed per minute and per kilogram of body weight per minute), we used the average of the two highest values in 30-second samples recorded during the final minutes of exercise. Venous blood was collected at two morning visits, after subjects had abstained from all food and drink, except water, for 12 to 16 hours and from vigorous activity for at least 12 hours, and was mixed with 1.5 mg of EDTA per milliliter. Aliquots of plasma were stored at -80°C for later assay of apolipoproteins. During one clinic visit, subjects consumed 75 g of glucose after the collection of fasting blood samples; venous blood was collected two hours later for the assessment of glucose tolerance.

Laboratory Procedures

Lipoprotein values at base line and at one year are reported as the means of two fasting values. Plasma levels of total cholesterol and triglycerides were measured by enzymatic procedures.^{16,17} HDL cholesterol was measured by dextran sulfate-magnesium precipitation,¹⁸ followed by enzymatic measurement of the non-precipitated cholesterol.¹⁶ Very-low-density lipoprotein (VLDL) cholesterol levels were calculated as the triglyceride level divided by 5,¹⁹ unless triglyceride levels exceeded 400 mg per deciliter (4.52 mmol per liter), in which case VLDL cholesterol was measured by enzymatic methods,¹⁶ after ultracentrifugation of serum for 18 hours.²⁰ LDL cholesterol was calculated as total cholesterol minus the sum of HDL cholesterol plus VLDL cholesterol.¹⁹ Values were consistently within specified limits as monitored by the Lipid Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute. Apolipoproteins A-I and B were measured by rate immunonephelometry (Array, Beckman, Brea, Calif).²¹ Plasma glucose was measured by National Health Laboratories, San Diego, California.

Assessment of Diet

At base line and at one year, the subjects completed five unannounced 24-hour dietary-recall questionnaires, in the form of computer-assisted telephone interviews, with use of two-dimensional food posters.²² Nutrient intake was calculated with use of Food Database software, versions 5A and 6A, and Nutrient Database software, version 2.4 (Minnesota Nutrition Data System, Nutrition Coordinating Center, University of Minnesota, Minneapolis).²³ Data for each period represent the mean of the data from four weekday and one weekend 24-hour dietary-recall records.

Statistical Analysis

Analysis of variance was used as a global test for differences in the degree of change from base-line values among groups, calculated separately for each sex. When the analysis of variance indicated significant differences between groups ($P < 0.05$), post hoc comparisons were made, with the Bonferroni adjustment of significance levels for six possible pairwise comparisons, at the

5 percent level of significance, in two-tailed tests (i.e., a P value <0.0083 for a given pair is reported as P<0.05 in this report). The log of the triglyceride level was used in the analyses, but the values are presented in common clinical units (milligrams per deciliter [millimoles per liter]).

RESULTS

The screening procedures excluded 421 of 789 women and 341 of 767 men because they had HDL cholesterol levels at or above 60 mg per deciliter or 45 mg per deciliter, respectively. An additional 111 women and 172 men did not meet the criteria for the LDL cholesterol or triglyceride level, 20 women and 11 men did not meet the criteria for blood pressure or glucose, and 35 women and 30 men chose not to continue with the screening. Of the remaining 202 women and 213 men who were eligible, 22 women and 16 men were excluded because they had positive or equivocal treadmill tests, and 180 women and 197 men therefore underwent randomization. Of these, 177 women (98 percent) and 190 men (96 percent) returned for lipid measurements at one year. Missing data for variables presented here were distributed evenly among the treatment groups; no more than three persons within a group had missing data for any given variable.

Tables 1 and 2 present means (\pm SD) for base-line values and changes in those values at one year in women and men, respectively, according to group, for dietary and fitness-related variables. Analysis of variance revealed no significant differences among the groups at base line in any variable listed in Table 1 or 2. The mean age was 56.9 ± 5.1 years for women and 47.8 ± 8.9 for men. For both sexes, caloric intake decreased significantly in the groups assigned to diet and diet plus exercise, as compared with the exercise group, but not as compared with the controls, and the degree of change in weight at one year did not differ significantly between the diet group and the diet-plus-exercise group.

Among the women, the composition of the diet was similar to that of the NCEP Step 1 diet¹¹ at base line in all groups and was not significantly changed at one year in the controls or the subjects assigned to exercise alone; both groups following the Step 2 diet significantly reduced the percentage of calories from total, saturated, and monounsaturated fat and cholesterol and achieved NCEP Step 2 goals. Among the men, the mean base-line fat intake slightly exceeded Step 1 goals in all groups, but the two groups following the diet reduced fat and cholesterol intake

TABLE 1. BASE-LINE VALUES FOR VARIABLES RELATED TO DIET AND FITNESS IN WOMEN AND CHANGES AT ONE YEAR, ACCORDING TO STUDY GROUP.*

| VARIABLE | BASE-LINE VALUE (N=177) | CHANGE AT ONE YEAR | | | | P VALUE† |
|------------------------------|----------------------------|-------------------------|--------------------------|----------------------|------------------------------------|-------------|
| | | CONTROL GROUP (N=45) | EXERCISE GROUP (N=43) | DIET GROUP (N=46) | DIET-PLUS-EXERCISE GROUP (N=43) | |
| Caloric intake (kcal/day) | 1814 \pm 494 | -19.3 \pm 367.1 | +53.8 \pm 409.6 | -220.2 \pm 355.8‡ | -191.2 \pm 343.2§ | 0.001 |
| Calories from nutrients (%) | | | | | | |
| Carbohydrates | 57.1 \pm 8.0 | -0.2 \pm 7.3 | -0.3 \pm 7.9 | +5.5 \pm 8.0‡¶ | +7.8 \pm 6.2 ** | <0.001 |
| Total fat | 28.4 \pm 7.1 | -0.2 \pm 6.7 | +0.3 \pm 6.9 | -5.7 \pm 7.4¶** | -8.0 \pm 5.8 ** | <0.001 |
| Saturated fat | 9.0 \pm 2.9 | +0.2 \pm 2.8 | +0.2 \pm 3.1 | -2.4 \pm 2.8 ** | -3.0 \pm 2.3 ** | <0.001 |
| Monounsaturated fat | 10.7 \pm 3.0 | +0.0 \pm 3.2 | +0.3 \pm 3.0 | -2.1 \pm 3.5‡‡‡ | -3.1 \pm 2.9 ** | <0.001 |
| Polyunsaturated fat | 6.4 \pm 1.9 | -0.3 \pm 2.4 | -0.2 \pm 2.5 | -0.9 \pm 2.3 | -1.5 \pm 1.7 | 0.04 |
| Cholesterol intake (mg/day) | 175.0 \pm 82.6 | +11.8 \pm 85.6 | +16.5 \pm 88.6 | -67.3 \pm 70.9 ** | -63.1 \pm 83.1 ** | <0.001 |
| Body weight (kg) | 69.6 \pm 10.5 | +0.8 \pm 4.2 | -0.4 \pm 2.5 | -2.7 \pm 3.5§ | -3.1 \pm 3.7‡ | <0.001 |
| Waist-to-hip ratio | 0.82 \pm 0.06 | -0.01 \pm 0.03 | -0.01 \pm 0.03 | -0.01 \pm 0.04 | -0.01 \pm 0.05 | 0.88 |
| $\dot{V}O_2$ max (ml/min) | 1790 \pm 356 | -54.6 \pm 179.1 | +150.1 \pm 211.6 | -66.9 \pm 261.0** | +152.2 \pm 202.6 ‡‡ | <0.001 |
| $\dot{V}O_2$ max (ml/kg/min) | 25.9 \pm 4.7 | -1.0 \pm 3.0 | +2.4 \pm 3.3 | +0.2 \pm 4.1§ | +3.7 \pm 3.8 ‡‡ | <0.001 |
| Treadmill time (min) | 14.6 \pm 3.3 | -0.1 \pm 2.0 | +2.1 \pm 1.9 | +0.8 \pm 1.8§ | +3.5 \pm 1.6‡ ‡‡ | <0.001 |

*Plus-minus values are means \pm SD. $\dot{V}O_2$ max denotes maximal oxygen consumption during a treadmill exercise test. P values for comparisons between groups have been adjusted for six pairwise comparisons (Bonferroni's adjustment). To convert caloric intake to kilojoules per day, multiply by 4.2.

†P values were derived by analysis of variance and denote the overall significance of differences among the four groups.

‡P<0.01 for the comparison with the exercise group.

§P<0.05 for the comparison with the exercise group.

¶P<0.01 for the comparison with the control group.

||P<0.001 for the comparison with the control group.

**P<0.001 for the comparison with the exercise group.

‡‡P<0.05 for the comparison with the control group.

‡‡‡P<0.001 for the comparison with the diet group.

significantly, as compared with the controls and the exercise group, and achieved Step 2 goals, whereas the composition of the diet was unchanged in the other groups. The mean base-line body-mass index was 26.3 ± 3.2 for the women and 27.0 ± 2.8 for the men. For women and men, significant weight loss occurred in both diet groups, as compared with the control and exercise groups, and changes in weight did not differ significantly between the diet and diet-plus-exercise groups or between patients assigned to exercise only and controls. Mean reductions in the waist-to-hip ratio were significant among the men assigned to diet plus exercise, as compared with the controls and those assigned to exercise only, but they did not differ significantly among the other groups. Women and men in both the exercise and the diet-plus-exercise groups had significantly increased maximal oxygen consumption as compared with the control and diet groups.

Tables 3 and 4 present base-line values and changes at one year, according to study group, for lipoprotein levels and other risk factors for coronary heart disease in women and men, respectively. Analysis of variance revealed no significant differences among the groups for any variable at base line (Tables 3 and 4) or for the ratio of LDL to HDL cholesterol

(3.5 ± 0.7 for women; 4.4 ± 0.7 for men). Significant changes in the HDL cholesterol level were not observed for either sex, nor were changes in triglyceride levels. Total and LDL cholesterol levels were significantly reduced among both women and men in the diet-plus-exercise group, as compared with the controls, and among men in the diet-plus-exercise group, as compared with the group assigned to exercise only. There were no significant reductions in total and LDL cholesterol levels for either sex in the diet group. Changes in the ratio of total to HDL cholesterol did not differ significantly among the groups for either sex, nor did changes in the ratio of LDL to HDL cholesterol among women ($P=0.39$ by analysis of variance). However, the LDL:HDL cholesterol ratio was significantly reduced among the men assigned to diet plus exercise (-0.6 ± 0.7), as compared with the controls (-0.1 ± 1.0 , $P<0.05$), but was not significantly changed in the exercise group (-0.2 ± 0.7) or among men in the diet group (-0.2 ± 0.6), as compared with the other groups ($P=0.01$ by analysis of variance).

Means of individual percentage changes in plasma HDL and LDL cholesterol levels are presented with 95 percent confidence intervals, for both sexes, in Figure 1. The percentage increases in HDL cholest-

TABLE 2. BASE-LINE VALUES FOR VARIABLES RELATED TO DIET AND FITNESS IN MEN AND CHANGES AT ONE YEAR, ACCORDING TO STUDY GROUP.*

| VARIABLE | BASE-LINE VALUE (N=190) | CHANGE AT ONE YEAR | | | | P VALUE† |
|------------------------------|----------------------------|-------------------------|--------------------------|----------------------|------------------------------------|-------------|
| | | CONTROL GROUP (N=46) | EXERCISE GROUP (N=47) | DIET GROUP (N=49) | DIET-PLUS-EXERCISE GROUP (N=48) | |
| Caloric intake (kcal/day) | 2421±588 | -24.5±481.5 | +140.7±437.2 | -285.2±540.6‡ | -166.8±516.1§ | <0.001 |
| Calories from nutrients (%) | | | | | | |
| Carbohydrates | 54.0±8.2 | +1.1±6.6 | +1.4±6.3 | +8.0±9.3‡¶ | +9.3±8.3‡¶ | <0.001 |
| Total fat | 30.4±7.0 | -0.7±5.9 | -0.5±5.7 | -8.0±8.1‡¶ | -8.2±5.9‡¶ | <0.001 |
| Saturated fat | 10.1±3.1 | +0.0±2.4 | -0.1±2.6 | -3.4±3.2‡¶ | -3.9±2.6‡¶ | <0.001 |
| Monounsaturated fat | 11.4±3.0 | +0.0±2.9 | +0.0±2.5 | -2.8±3.4‡¶ | -2.9±2.6‡¶ | <0.001 |
| Polyunsaturated fat | 6.5±1.8 | -0.7±1.7 | -0.3±1.9 | -1.3±2.2 | -0.9±2.1 | 0.13 |
| Cholesterol intake (mg/day) | 256.1±123.5 | -3.8±121.9 | +7.9±99.0 | -101.8±130.5‡¶ | -110.2±106.6‡¶ | <0.001 |
| Body weight (kg) | 84.2±10.8 | +0.5±2.7 | -0.6±3.1 | -2.8±3.5§¶ | -4.2±4.2‡¶ | <0.001 |
| Waist-to-hip ratio | 0.94±0.05 | -0.01±0.04 | -0.01±0.03 | -0.02±0.03 | -0.03±0.04§¶ | 0.003 |
| $\dot{V}O_2$ max (ml/min) | 3100±516 | -45.9±257.9 | +141.6±301.1 | -55.2±274.2** | +219.5±287.0¶†† | <0.001 |
| $\dot{V}O_2$ max (ml/kg/min) | 37.5±6.7 | -0.8±3.4 | +1.9±4.3 | +0.4±4.0 | +4.7±4.8§¶†† | <0.001 |
| Treadmill time (min) | 19.3±3.1 | +0.6±1.7 | +1.9±2.1 | +1.0±1.7 | +2.9±2.5¶†† | <0.001 |

*Plus-minus values are means \pm SD. $\dot{V}O_2$ max denotes maximal oxygen consumption during a treadmill exercise test. P values for comparisons between groups have been adjusted for six pairwise comparisons (Bonferroni's adjustment). To convert caloric intake to kilojoules per day, multiply by 4.2.

†P values were derived by analysis of variance and denote the overall significance of differences among the four groups.

‡P<0.001 for the comparison with the exercise group.

§P<0.05 for the comparison with the exercise group.

¶P<0.001 for the comparison with the control group.

||P<0.05 for the comparison with the control group.

**P<0.01 for the comparison with the exercise group.

††P<0.001 for the comparison with the diet group.

terol levels among both women and men in the exercise group did not reach statistical significance as compared with the changes in the other groups. There was a significant reduction in the LDL cholesterol level among women in the diet-plus-exercise group, as compared with the controls, and among men in the diet-plus-exercise group, as compared with those in the control group and the exercise group, but the change was not significant among either men or women in the diet group as compared with the other groups.

As Table 3 shows, the level of apolipoprotein A-I was significantly reduced among women in the diet-plus-exercise group, as compared with those in the exercise group, whereas changes in apolipoprotein B levels did not differ significantly among the women in the various groups. In contrast, the level of apolipoprotein B was significantly reduced among men in the diet-plus-exercise group, as compared with those in the exercise and control groups, whereas changes in apolipoprotein A-I levels in men did not differ significantly among the groups (Table 4). The degree of change in fasting and two-hour (post-challenge) glucose levels did not differ significantly among the groups for either sex. The resting heart

rate was significantly lower among both sexes in the diet-plus-exercise group than in the control group. Resting diastolic blood pressure was also lower among the men in the diet-plus-exercise group than among the men in the control group.

DISCUSSION

This study extends our previous investigations of the effects of diet, exercise, and weight loss on plasma lipoprotein levels in overweight men^{9,10} and premenopausal women¹⁰ to men and postmenopausal women who are at high risk for coronary heart disease because they have low HDL cholesterol levels and moderately elevated LDL cholesterol levels. We restricted the study to persons with LDL cholesterol levels at which drug therapy is not recommended before an attempt is made to lower LDL cholesterol levels through long-term reduction of dietary fat, particularly saturated fat.^{6,11} We wanted to determine whether changes in the diet would further reduce HDL cholesterol levels, thereby potentially increasing, rather than decreasing, the risk of coronary heart disease, and whether the addition of aerobic exercise to the Step 2 diet would offset this adverse effect, as we previously demonstrated in a study of

TABLE 3. BASE-LINE VALUES FOR RISK FACTORS FOR CORONARY HEART DISEASE IN WOMEN AND CHANGES AT ONE YEAR, ACCORDING TO STUDY GROUP.*

| VARIABLE | BASE-LINE VALUE (N=177) | CHANGE AT ONE YEAR | | | | P VALUE† |
|--------------------------------|----------------------------|-------------------------|--------------------------|----------------------|------------------------------------|-------------|
| | | CONTROL GROUP (N=45) | EXERCISE GROUP (N=43) | DIET GROUP (N=46) | DIET-PLUS-EXERCISE GROUP (N=43) | |
| Lipids (mg/dl)‡ | | | | | | |
| HDL cholesterol | 47.0±6.7 | +1.0±6.1 | +2.3±6.7 | +0.3±6.0 | -1.1±6.4 | 0.09 |
| LDL cholesterol | 160.7±18.4 | -2.5±16.6 | -5.6±19.4 | -7.3±18.9 | -14.5±22.2§ | 0.03 |
| Total cholesterol | 239.4±24.9 | -1.0±19.5 | -5.7±22.9 | -7.9±20.6 | -17.5±21.4¶ | 0.004 |
| Total:HDL cholesterol ratio | 5.2±1.0 | -0.0±0.7 | -0.4±0.8 | -0.2±0.7 | -0.2±0.8 | 0.25 |
| Triglycerides | 158.8±72.2 | +2.1±42.4 | -12.2±44.8 | -4.2±65.1 | -10.3±49.6 | 0.55 |
| Apolipoprotein A-I | 133.2±16.4 | +3.2±14.6 | +4.9±15.9 | -1.0±17.2 | -4.4±13.2 | 0.02 |
| Apolipoprotein B | 127.0±19.8 | +0.0±13.4 | -3.0±15.8 | -2.1±16.6 | -7.4±15.0 | 0.16 |
| Glucose (mg/dl)** | | | | | | |
| Fasting | 93.7±8.7 | -2.6±15.2 | -6.2±8.3 | -7.7±6.6 | -7.7±10.4 | 0.08 |
| 2-Hr | 103.5±30.3 | -3.3±28.4 | -0.0±22.2 | -10.7±24.6 | -9.4±28.9 | 0.20 |
| Resting blood pressure (mm Hg) | | | | | | |
| Systolic | 115.5±12.8 | -2.4±7.6 | -1.1±8.9 | -3.5±9.2 | -3.1±8.4 | 0.59 |
| Diastolic | 73.2±7.4 | -0.6±5.9 | -1.4±5.9 | -1.9±5.0 | -2.7±4.6 | 0.33 |
| Resting heart rate (beats/min) | 67.0±7.1 | +1.1±5.9 | -0.8±7.3 | -1.6±6.9 | -3.8±6.7¶ | 0.01 |

*Plus-minus values are means ±SD. P values for comparisons between groups have been adjusted for six pairwise comparisons (Bonferroni's adjustment).

†P values were derived by analysis of variance and denote the overall significance of differences among the four groups.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

§P<0.05 for the comparison with the control group.

¶P<0.01 for the comparison with the control group.

||P<0.05 for the comparison with the exercise group.

**To convert values for glucose to millimoles per liter, multiply by 0.05551. Two-hour values were measured two hours after the administration of 75 g of glucose.

overweight men and premenopausal women.¹⁰ In the current study, the NCEP Step 2 diet failed to reduce LDL cholesterol levels significantly in either men or women as compared with controls; when the diet was combined with aerobic exercise, however, the resulting reductions in LDL cholesterol levels were significant, with no adverse effects on HDL cholesterol.

On average, both the women and men who were eligible for this study had initial dietary fat intakes that approximated those in the NCEP Step 1 diet, a fact that may have contributed to their low HDL cholesterol levels. Nonetheless, their base-line LDL cholesterol levels would prompt a physician following the NCEP guidelines to recommend dietary therapy to achieve a Step 2 diet.¹¹ Our results suggest that the stepped dietary approach of the NCEP is unlikely by itself to result in substantial reductions in LDL cholesterol levels, particularly since many patients will not be provided with a dietary program as comprehensive as that used here. It is worth rec-

ognizing, however, that the NCEP guidelines stress the importance of further reductions in the dietary intake of fat and cholesterol. It may be that greater emphasis on increased consumption of certain foods, such as grains, fruits, and vegetables, would yield a different result.

Concern that substantial reductions in dietary fat content (to 20 to 22 percent of calories), with a reciprocal increase in carbohydrate intake, will raise triglyceride levels²⁴ or impair glucose tolerance²⁵ was not supported in this trial, possibly because of weight loss in the groups that followed the Step 2 diet. Therefore, adoption of the NCEP Step 2 diet does not appear to be associated with these risk factors in euglycemic women or men with low HDL cholesterol levels and elevated LDL cholesterol levels. Nonetheless, the recommendation of a low-fat, high-carbohydrate diet remains controversial.^{26,27}

Most data supporting the widespread belief that lowering dietary fat and cholesterol will reduce LDL cholesterol levels are derived from observational and

TABLE 4. BASE-LINE VALUES FOR RISK FACTORS FOR CORONARY HEART DISEASE IN MEN AND CHANGES AT ONE YEAR, ACCORDING TO STUDY GROUP.*

| VARIABLE | BASE-LINE VALUE (N=190) | CHANGE AT ONE YEAR | | | | P VALUE† |
|--------------------------------|----------------------------|-------------------------|--------------------------|----------------------|------------------------------------|-------------|
| | | CONTROL GROUP (N=46) | EXERCISE GROUP (N=47) | DIET GROUP (N=49) | DIET-PLUS-EXERCISE GROUP (N=48) | |
| Lipids (mg/dl)‡ | | | | | | |
| HDL cholesterol | 35.8±4.4 | -0.2±4.3 | +1.2±4.4 | -0.8±4.4 | +0.4±5.3 | 0.21 |
| LDL cholesterol | 155.8±14.2 | -4.6±21.1 | -3.6±18.8 | -10.8±18.8 | -20.0±17.3§¶ | <0.001 |
| Total cholesterol | 226.0±20.1 | -3.9±21.6 | -5.2±20.5 | -13.2±19.3 | -20.6±20.0§ | <0.001 |
| Total:HDL cholesterol ratio | 6.4±1.1 | -0.1±1.0 | -0.3±1.0 | -0.2±0.9 | -0.6±0.9 | 0.07 |
| Triglycerides | 171.1±69.1 | +8.6±83.3 | -13.5±50.8 | -6.3±59.7 | -7.0±55.3 | 0.39 |
| Apolipoprotein A-I | 113.9±10.4 | +1.8±9.1 | +0.4±10.2 | -2.5±8.7 | +0.5±10.6 | 0.16 |
| Apolipoprotein B | 123.2±15.4 | +0.0±14.8 | -1.4±14.7 | -5.8±14.2 | -10.2±17.9**†† | 0.008 |
| Glucose (mg/dl)‡‡ | | | | | | |
| Fasting | 96.2±8.8 | -3.8±10.5 | -7.1±9.3 | -7.6±8.6 | -7.8±8.8 | 0.13 |
| 2-Hr | 97.9±30.3 | -5.8±28.3 | -3.3±25.2 | -18.3±25.2 | -15.1±29.7 | 0.02 |
| Resting blood pressure (mm Hg) | | | | | | |
| Systolic | 114.3±11.4 | +0.3±7.9 | -0.6±7.3 | -1.7±6.4 | -3.0±6.8 | 0.13 |
| Diastolic | 76.1±7.4 | +1.8±6.1 | -1.1±7.1 | -0.3±5.2 | -3.0±6.6§§ | 0.003 |
| Resting heart rate (beats/min) | 65.2±8.6 | +0.8±5.9 | -2.9±6.2** | -0.9±5.6 | -5.8±7.9§¶¶ | <0.001 |

*Plus-minus values are means ±SD. P values for comparisons between groups have been adjusted for six pairwise comparisons (Bonferroni's adjustment).

†P values were derived by analysis of variance and denote the overall significance of differences among the four groups.

‡To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

§P<0.001 for the comparison with the control group.

¶P<0.001 for the comparison with the exercise group.

||P<0.01 for the comparison with the exercise group.

**P<0.05 for the comparison with the control group.

††P<0.05 for the comparison with the exercise group.

‡‡To convert values for glucose to millimoles per liter, multiply by 0.05551. Two-hour glucose values were measured two hours after the administration of 75 g of glucose.

§§P<0.01 for the comparison with the control group.

¶¶P<0.01 for the comparison with the diet group.

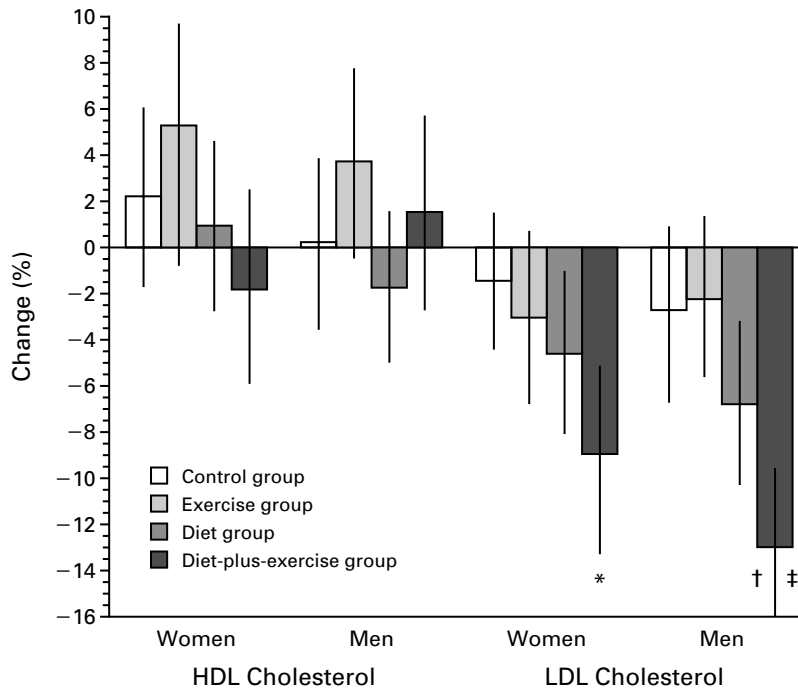


Figure 1. Mean Changes in Plasma HDL Cholesterol and LDL Cholesterol Levels in the Study Groups at One Year.

The vertical lines represent 95 percent confidence intervals. Significance levels, after Bonferroni's adjustment for the six pairwise comparisons, are indicated as follows: the asterisk denotes $P < 0.05$ for the comparison with the control group, the dagger $P < 0.001$ for the comparison with the control group, and the double dagger $P < 0.001$ for the comparison with the exercise group.

cross-sectional population studies and studies conducted in institutional settings or metabolic wards,^{6,8,11,28} rather than under conditions of clinical practice (i.e., among people living in the community who choose their own foods). Under such conditions, Hunninghake et al. observed no change in the LDL:HDL cholesterol ratio in men and women who initially had high LDL cholesterol levels while consuming the NCEP Step 2 diet, as compared with their levels while consuming a high-fat, high-cholesterol diet, during which levels of both LDL cholesterol and HDL cholesterol were reduced.⁷ In addition, HDL cholesterol levels were lowered, along with the levels of LDL cholesterol and apolipoprotein B, in men with hypercholesterolemia when dietary fat was reduced from a base-line level of 34 to 36 percent of total calories from fat to 22 to 25 percent.²⁴

In our previous controlled study of moderately overweight men and premenopausal women with a high-fat base-line diet, a weight-reducing NCEP Step 1 diet failed to reduce LDL cholesterol levels significantly in men, with or without exercise, as compared with a control group, but it did significantly reduce LDL cholesterol levels in women. HDL cholesterol levels were significantly reduced in

the women who made only dietary changes, however, as compared with those who also exercised, despite the fact that there was no greater weight loss with the addition of exercise.¹⁰ Among men, the addition of aerobic exercise produced greater weight loss and significant elevation of the HDL cholesterol level; this effect was not seen with diet alone. The LDL:HDL cholesterol ratio was significantly lowered, as compared with that in the control group, among the men assigned to dietary changes alone, but not among the women, whereas this ratio was lowered in both men and women assigned to diet plus exercise.

In the current study of men and postmenopausal women with elevated LDL cholesterol levels and low HDL cholesterol levels at base line, a reduction of about 8 percent in dietary fat intake was achieved, as in our previous study,¹⁰ but the reductions in LDL cholesterol levels were not significant for either sex without the addition of exercise. Although even small reductions in LDL cholesterol levels may yield epidemiologically important reductions in the risk of coronary heart disease, these findings demonstrate the importance of an exercise program when diet alone has not adequately reduced LDL cholesterol

levels. Furthermore, the benefits of exercise in terms of the reduction in the risk of cardiovascular disease extend far beyond improvements in the lipoprotein profile,²⁹ and increased physical activity is now recommended for patients at all cholesterol levels.¹¹

An interesting question is how the addition of exercise enhanced the effects of diet on LDL cholesterol. The diet-plus-exercise group may have adhered more closely to the diet than the group assigned to the diet alone; however, analyses of nutrients listed in multiple 24-hour dietary-recall records showed no significant differences in mean values between the two groups that followed the diet, for either sex. Furthermore, the amount of weight loss did not differ significantly between the groups assigned to the diet, and the slightly greater weight loss among men and women in the diet-plus-exercise group could have been due to increased energy expenditure. The combination of reduced dietary fat and increased use of energy from fat through exercise may create a physiologic state that is particularly beneficial to lipid metabolism even in the absence of weight loss.^{30,31}

The fact that weight loss did not differ significantly between the diet group and diet-plus-exercise group suggests that the amount of exercise achieved in the diet-plus-exercise group was not great enough to increase weight loss. The absence of weight loss in the exercise group may explain why the HDL cholesterol levels were not significantly improved in these groups, since weight loss may be a crucial factor in the increases in HDL cholesterol levels observed with exercise,³⁰⁻³³ whether weight loss is achieved solely by caloric restriction or by increased physical activity, with no dietary change.⁹ Greater weight loss might also have produced a greater reduction in LDL cholesterol levels. Although LDL cholesterol levels were not reduced even among men with substantial weight loss in either of our previous randomized, controlled trials,^{9,10} reductions in LDL cholesterol levels have been associated with weight loss in other studies.³⁴

In conclusion, these data strongly support recommendations¹¹ to add exercise to diet for the management of lipoprotein levels associated with a high risk of coronary heart disease. Together with our previous findings,^{9,10} they suggest that weight loss should be further emphasized, when appropriate, particularly in counseling men and women who have both low HDL cholesterol levels and elevated LDL cholesterol levels.

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