

EFFECTS OF THE AMOUNT AND INTENSITY OF EXERCISE ON PLASMA LIPOPROTEINS

WILLIAM E. KRAUS, M.D., JOSEPH A. HOUMARD, PH.D., BRIAN D. DUSCHA, M.S., KENNETH J. KNETZGER, M.S.,
MICHELLE B. WHARTON, M.A., JENNIFER S. MCCARTNEY, M.A., CONNIE W. BALES, PH.D., R.D., SARAH HENES, R.D.,
GREGORY P. SAMSA, PH.D., JAMES D. OTVOS, PH.D., KRISHNAJI R. KULKARNI, PH.D., AND CRIS A. SLENTZ, PH.D.

ABSTRACT

Background Increased physical activity is related to reduced risk of cardiovascular disease, possibly because it leads to improvement in the lipoprotein profile. However, the amount of exercise training required for optimal benefit is unknown. In a prospective, randomized study, we investigated the effects of the amount and intensity of exercise on lipoproteins.

Methods A total of 111 sedentary, overweight men and women with mild-to-moderate dyslipidemia were randomly assigned to participate for six months in a control group or for approximately eight months in one of three exercise groups: high-amount–high-intensity exercise, the caloric equivalent of jogging 20 mi (32.0 km) per week at 65 to 80 percent of peak oxygen consumption; low-amount–high-intensity exercise, the equivalent of jogging 12 mi (19.2 km) per week at 65 to 80 percent of peak oxygen consumption; or low-amount–moderate-intensity exercise, the equivalent of walking 12 mi per week at 40 to 55 percent of peak oxygen consumption. Subjects were encouraged to maintain their base-line body weight. The 84 subjects who complied with these guidelines served as the basis for the main analysis. Detailed lipoprotein profiling was performed by nuclear magnetic resonance spectroscopy with verification by measurement of cholesterol in lipoprotein subfractions.

Results There was a beneficial effect of exercise on a variety of lipid and lipoprotein variables, seen most clearly with the high amount of high-intensity exercise. The high amount of exercise resulted in greater improvements than did the lower amounts of exercise (in 10 of 11 lipoprotein variables) and was always superior to the control condition (11 of 11 variables). Both lower-amount exercise groups always had better responses than the control group (22 of 22 comparisons).

Conclusions The highest amount of weekly exercise, with minimal weight change, had widespread beneficial effects on the lipoprotein profile. The improvements were related to the amount of activity and not to the intensity of exercise or improvement in fitness. (N Engl J Med 2002;347:1483-92.)

Copyright © 2002 Massachusetts Medical Society.

INCREASED physical activity and fitness are clearly associated with reductions in the risk of cardiovascular disease,¹⁻⁵ but the optimal intensity or amount of exercise necessary for reductions in risk or risk factors is unknown. Because of apparently conflicting information,¹⁻³ there is confusion about what recommendations to make for exercise that will confer specific health benefits. In spite of the importance of this issue, there have been no prospective studies investigating the effects of different amounts and intensities of exercise.

Although regular exercise is known to decrease the risk of cardiovascular disease, comprehensive reviews^{6,7} suggest that exercise has little effect on total cholesterol or low-density lipoprotein (LDL) cholesterol concentrations and only a minimal and inconsistent beneficial effect on high-density lipoprotein (HDL) cholesterol concentrations.⁶ Thus, there are two deficiencies in the current knowledge in this area. First, the ability to draw conclusions about the relation between exercise and lipids is compromised by the lack of prospective, randomized exercise studies comparing at least two different amounts of exercise.⁶ Second, it is now clear that the concentrations of LDL particles, small LDL particles, large HDL particles, and large very-low-density lipoprotein (VLDL) particles are better indicators of cardiovascular risk than are the elements of the traditional lipid profile.⁸⁻¹⁷

The purpose of the Studies of Targeted Risk Reduction Interventions through Defined Exercise (STRRIDE), a randomized, controlled clinical study, was to investigate the effects of the amount and intensity of exercise on risk factors for cardiovascular disease in overweight and obese men and women with mild-to-moderate dyslipidemia. Here we report the effects on serum lipoproteins.

From the Divisions of Cardiology (W.E.K., B.D.D., K.J.K., C.A.S.), Geriatrics (C.W.B., S.H.), and General Internal Medicine (G.P.S.), Department of Medicine, the Duke Center for Living (W.E.K.), the Center for Health Policy Research (G.P.S.), and the Department of Community and Family Medicine (G.P.S.), Duke University Medical Center; and the Geriatric Research, Education, and Clinical Center, Durham Veterans Affairs Medical Center (C.W.B.) — both in Durham, N.C.; the Department of Exercise and Sport Science and the Human Performance Laboratory, East Carolina University, Greenville, N.C. (J.A.H., M.B.W., J.S.M.); LipoScience, Cary, N.C. (J.D.O.); and Atherotech, Birmingham, Ala. (K.R.K.). Address reprint requests to Dr. Kraus at the Division of Cardiology, Department of Medicine, P.O. Box 3327, Duke University Medical Center, Durham, NC 27710, or at william.kraus@duke.edu.

METHODS

Study Design

A complete description of the design of the study has been published elsewhere.¹⁸ The research protocol was reviewed and approved by the relevant institutional review boards.

Study Subjects

After giving written, informed consent, 159 subjects, 40 to 65 years of age, who were sedentary, were overweight or mildly obese (body-mass index [the weight in kilograms divided by the square of the height in meters], 25 to 35), and had dyslipidemia (either an LDL cholesterol concentration of 130 to 190 mg per deciliter [3.4 to 4.9 mmol per liter] or an HDL cholesterol concentration below 40 mg per deciliter [1.0 mmol per liter] for men or below 45 mg per deciliter [1.2 mmol per liter] for women), were randomly assigned to one of three exercise groups or a nonexercising control group. Subjects were recruited continuously between January 1999 and June 2000, and the exercise program was completed by April 2001. Of the 159 randomized subjects, 48 (30.2 percent) dropped out of the study, 15 (9.4 percent) had an excessively low rate of adherence to exercise, 10 (6.3 percent) had incomplete lipid data, and 2 (1.3 percent) had excessive weight loss, leaving 84 subjects in the main analysis.

Exercise Training

The exercise prescriptions in the three exercise groups were as follows: high-amount–high-intensity exercise, the caloric equivalent of jogging approximately 20 mi (32.0 km) per week for a person weighing 90 kg (range, 19.2 to 20.6 mi [30.7 to 33.0 km] per week for a person weighing 70 to 110 kg)¹⁹ at 65 to 80 percent of peak oxygen consumption; low-amount–high-intensity exercise, the caloric equivalent of jogging approximately 12 mi (19.2 km) per week at 65 to 80 percent of peak oxygen consumption; and low-amount–moderate-intensity exercise, the caloric equivalent of walking approximately 12 mi per week at 40 to 55 percent of peak oxygen consumption. For the subjects in the high-amount–high-intensity group, the specific prescription was to expend 23 kcal per kilogram of body weight per week; subjects in the two low-amount groups were to expend 14 kcal per kilogram per week. The machines used for exercise included cycle ergometers, treadmills, and elliptical trainers. There was an initial period of two to three months during which the amount and intensity of exercise were gradually increased, followed by six months at the appropriate exercise prescription. All exercise sessions were verified by direct supervision or by heart-rate monitors that provided recorded data (Polar Electro).

Dietary Evaluations and Control of Body Weight

Nutrient intakes were determined at base line and at the end of the study. To minimize the confounding effects of weight loss, subjects were counseled to maintain body weight, which we believed to be ethically justified by the short time frame of the study. Data were excluded from the primary analysis for subjects whose weight varied by more than 5 percent from base line to the end of the study.

Lipids and Lipoproteins

Fasting plasma samples were analyzed by LipoScience for lipoprotein profiling by nuclear magnetic resonance spectroscopy. Each measurement includes the concentrations of six subclasses of VLDL, four subclasses of LDL (including intermediate-density lipoprotein [IDL]), and five subclasses of HDL, as well as the calculated weighted average sizes of VLDL, LDL, and HDL particles, the concentration of LDL particles, and estimates of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol concentrations.^{20,21} Since the nuclear magnetic resonance imaging method measures lipoprotein particles rather than cholesterol, we sought verification of findings using a method that directly meas-

ures cholesterol in lipoprotein fractions separated by density-gradient ultracentrifugation.²² Samples from 20 subjects (10 men and 10 women) in the high-amount–high-intensity group and 20 subjects in the control group were analyzed by Atherotech (Birmingham, Ala.) with the Vertical Auto Profile method.²² All samples sent for lipid and lipoprotein analysis did not indicate the treatment-group assignment of the subject.

Intention-to-Treat Analysis

The goal of our study was to determine the physiological effects of specific, well-defined amounts and intensities of exercise on risk factors for cardiovascular disease. The study was specifically designed to address the questions of “How much exercise is enough?” and “What is the optimal amount of exercise?” with respect to potentially beneficial effects on cardiovascular health and disease. To these ends, and in order to maintain clear separations of the levels of exercise among the exercise groups, we defined acceptable compliance rates for subjects in all exercise groups a priori to be between 74 percent and 115 percent of the assigned amount of exercise, thus permitting study of the relation between the actual level of exercise (not necessarily the intention to exercise) on various health-related variables. For similar reasons related to the effects of weight on lipoproteins, we also excluded subjects from the main analysis if they had a change in weight of more than 5 percent over the course of the study. Nevertheless, there may be clinical implications of an intention-to-treat analysis, and we therefore also report the results of such an analysis including all 101 subjects who had complete lipid data, irrespective of compliance or weight change.

Statistical Analysis

For the main analysis, we used analysis of variance (Statview or SAS software) followed by post hoc analysis. Unless indicated, only the results of post hoc analyses are reported. Because of the primary a priori interest, only differences between each exercise group and the control group were analyzed. An alpha error of less than 0.0167 was considered to indicate statistical significance, because of Bonferroni's correction.

To test for hypothesized effects of the amount and intensity of exercise, we used a multivariate analysis of variance to test for differences between the groups with regard to the entire set of 11 variables. We then ranked (for each variable) the groups with different amounts of exercise and, separately, the groups with different intensities of exercise. The group with the largest improvement was ranked first, and so on.

RESULTS

Base-line characteristics of the subjects are presented in Table 1. There were no significant differences among the groups in terms of demographic variables or in terms of initial fitness, total caloric intake, or macronutrient intake. Subjects who dropped out of the study were not significantly different from those who remained in the exercise or control groups in terms of age, height, weight, or body-mass index (data not shown).

Level of Exercise and Fitness Responses

A description of the exercise prescriptions and the effects of exercise on body weight, cardiovascular fitness (peak oxygen consumption), and nutrient intake are also shown in Table 1. In spite of the monitoring of body weight and the recommendation to maintain body weight, subjects in the high-amount–high-inten-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE SUBJECTS, CHARACTERISTICS OF THEIR EXERCISE PROGRAMS, AND CHANGES IN BODY WEIGHT, FITNESS, AND NUTRIENT INTAKE.*

| VARIABLE | ALL SUBJECTS (N=84) | CONTROL GROUP (N=26) | LOW-AMOUNT- MODERATE-INTENSITY GROUP (N=19) | LOW-AMOUNT- HIGH-INTENSITY GROUP (N=17) | HIGH-AMOUNT- HIGH-INTENSITY GROUP (N=22) |
|---|------------------------|-------------------------|---|---|--|
| Base-line characteristics | | | | | |
| Age — yr | 52.3±7.8 | 50.5±7.5 | 54.3±10.6 | 51.8±6.6 | 53.0±5.6 |
| Height — m | 1.72±0.10 | 1.70±0.11 | 1.75±0.10 | 1.71±0.09 | 1.72±0.10 |
| Weight — kg | 86.8±15.1 | 84.1±16.5 | 89.8±16.2 | 87.1±14.9 | 87.3±12.7 |
| Body-mass index | 29.3±3.0 | 29.0±3.3 | 29.2±2.8 | 29.6±3.2 | 29.4±2.8 |
| Race — no. (%) | | | | | |
| White | 68 (81) | 18 (69) | 17 (89) | 14 (82) | 19 (86) |
| Black | 15 (18) | 8 (31) | 2 (11) | 3 (18) | 2 (9) |
| Asian | 1 (1) | 0 | 0 | 0 | 1 (5) |
| Sex | | | | | |
| Female | 35 | 11 | 5 | 8 | 11 |
| Male | 49 | 15 | 14 | 9 | 11 |
| Peak oxygen consumption — ml/kg of body weight/min† | 29.2±6.3 | 28.5±7.0 | 30.8±7.3 | 29.5±6.1 | 28.1±4.9 |
| Food intake — kcal/day‡ | 2087±651 | 2089±676 | 2059±669 | 2137±659 | 2071±664 |
| Carbohydrates — % | 49.1±9.2 | 50.4±9.5 | 48.6±9.2 | 49.3±9.3 | 48.0±9.4 |
| Fat — % | 33.3±7.2 | 32.2±7.4 | 33.0±7.3 | 34.6±7.2 | 33.9±7.3 |
| Protein — % | 15.8±4.6 | 15.6±4.7 | 15.9±4.7 | 15.3±4.6 | 16.5±4.7 |
| Prescribed and actual amount and intensity of exercise | | | | | |
| Intensity range — percentage of peak oxygen consumption | | | 40–55 | 65–80 | 65–80 |
| Prescribed amount — mi/wk§ | | | 12 | 12 | 20 |
| Prescribed time — min/wk | | | 191±41 | 125±26 | 200±38 |
| Rate of adherence — % | | | 92.1±9.9 | 91.3±10.6 | 86.8±8.7 |
| Actual amount — mi/wk¶ | | | 11.1 | 11.0 | 17.4 |
| Actual time — min/wk | | | 176±36 | 117±26 | 174±35 |
| Frequency — no. of sessions/wk | | | 3.4±0.6 | 3.0±0.5 | 3.8±0.7 |
| Changes from base line | | | | | |
| Body weight — kg | | 0.95±3.04 | -0.55±1.80** | -0.17±1.79 | -1.52±2.16†† |
| Peak oxygen consumption | | | | | |
| Liters/min | | 0.02±0.18 | 0.16±0.15‡‡ | 0.41±0.14†† | 0.43±0.24†† |
| Percentage change | | 1.0±6.8 | 6.9±7.6§§ | 16.7±5.6†† | 17.8±9.0†† |
| Caloric intake — kcal/day | | 15.3±561 | 30.9±544 | -264.0±552 | -30.5±540 |
| Carbohydrate intake — % | | 0.0±10.7 | -3.3±10.4 | -3.6±10.5 | 1.1±10.3 |
| Fat intake — % | | 0.7±9.5 | 0.7±9.2 | 2.0±9.3 | 0.4±9.1 |
| Protein intake — % | | -0.4±5.2 | 2.2±5.0 | 1.2±5.1 | -1.3±5.0 |

*Plus-minus values are means ±SD. There were no significant differences among the groups in any demographic characteristic.

†Because of technical difficulties, means for peak oxygen consumption are based on data for 16 subjects in the control group, 13 in the low-amount-moderate-intensity group, 12 in the low-amount-high-intensity group, and 14 in the high-amount-high-intensity groups.

‡Percentages from carbohydrates, fat, and protein do not total 100 since ethanol calories are not included.

§Data are the approximate number of miles per week that are calorically equivalent to the prescribed 14 kcal per kilogram per week for the low-amount groups and 23 kcal per kilogram per week for the high-amount group.

¶Data are the prescribed amount multiplied by the rate of adherence for each group; therefore, there are no standard deviations given.

||Data are the prescribed time multiplied by the rate of adherence for each subject.

**P=0.04 for the comparison with the control group.

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

‡‡P=0.03 for the comparison with the control group.

§§P=0.02 for the comparison with the control group.

sity and low-amount-moderate intensity groups had weight loss that was small but significantly greater than that among controls. The high-amount-high-intensity and low-amount-high-intensity groups had similar increases in peak oxygen consumption (17.8 percent and 16.7 percent, respectively; P<0.001 for both

comparisons with the control group), implying that the intensity of exercise is more important than the amount of exercise in terms of increasing the level of fitness. There were no significant differences among groups in terms of changes in caloric consumption or the percentage of calories from macronutrients.

Base-Line Differences and Outliers

Lipoprotein data obtained at base line and at the end of the study are shown in Table 2. The low-amount–moderate-intensity group had significantly higher base-line concentrations of triglycerides and large VLDL particles than did controls. When the data were inspected for outliers, three subjects in the low-amount–moderate-intensity group were identified. When subsequent analyses were performed both with and without these subjects, the overall interpretation of the data was unchanged. Therefore, data from all qualifying subjects were included in all analyses.

Effects of Exercise on Lipoproteins

Exercise training had no significant effect on the total cholesterol or LDL cholesterol concentrations (data not shown). It did, however, have important effects on the concentrations of LDL subfractions (Fig. 1). High-amount–high-intensity exercise significantly reduced the concentrations of LDL and small LDL particles and increased the average size of LDL particles. The IDL cholesterol concentration decreased nonsignificantly with increasing exercise levels. Although both low-amount groups had improvements in these variables as compared with controls, only the effect on the size of LDL particles was significant for the low-amount–high-intensity group. There was a progressive effect of the amount of exercise on all four of the variables shown in Figure 1.

This effect of the amount of exercise was also seen for HDL variables, as shown in Figure 2. There was a clear beneficial effect ($P < 0.0167$) on the HDL cholesterol concentration in the high-amount–high-intensity group. The lower amount of exercise had smaller (nonsignificant) effects on these variables, with no apparent effect of the intensity of exercise.

In the high-amount–high-intensity, low-amount–high-intensity, and low-amount–moderate-intensity groups, there was improvement in triglyceride concentration ($P = 0.006$, $P = 0.07$, and $P < 0.001$, respectively), concentration of VLDL triglycerides ($P = 0.004$, $P = 0.04$, and $P < 0.001$, respectively), concentration of large VLDL particles ($P = 0.05$, $P = 0.13$, and $P < 0.001$, respectively), and size of VLDL particles ($P = 0.06$, $P = 0.005$, and $P < 0.001$, respectively).

Ranked Effects of the Intensity and Amount of Exercise

The ranked effects of the amount and intensity of exercise are shown in Table 3. The test for overall differences among groups was statistically significant according to multivariate analysis of variance ($P = 0.03$), providing a rationale for examining the effect of the amount of exercise. High-amount–high-intensity exercise had a larger effect on 10 of the 11 variables than did low-amount–high-intensity exercise. In turn, low-amount–high-intensity exercise had a beneficial effect

on all 11 variables, as judged by comparisons with the control group. These findings demonstrate a clear effect of the amount of exercise: in 21 of 22 cases, the higher the level of exercise, the greater the effect on lipid measures. The rankings of the levels of intensity show that neither low-amount–high-intensity exercise nor low-amount–moderate-intensity exercise was clearly superior in its effects on lipoproteins. The data therefore suggest that there is no clear effect of the intensity of exercise. However, both low-amount groups ranked above the control group on all 11 variables.

Intention-to-Treat Analysis

The conclusions from the intention-to-treat analyses (Table 4) were nearly identical to those from the primary analysis. In some cases, the intention-to-treat analysis revealed significant differences ($P < 0.0167$) between groups in comparisons for which only nonsignificant differences were found in the primary analysis. Conversely, in no case did the intention-to-treat analysis yield nonsignificant differences for comparisons that yielded statistically significant differences in the primary analysis. In sum, an intention-to-treat analysis would have provided stronger evidence than the primary analysis did of the benefits of high-amount–high-intensity exercise over the control condition. For example, according to the intention-to-treat analysis, $P = 0.002$ for the comparison between the high-amount–high-intensity group and the control group in terms of the concentration of small LDL particles, $P = 0.001$ for the comparison of the size of LDL particles, $P = 0.02$ for the comparison of the concentration of LDL particles, $P = 0.06$ for the comparison of the IDL cholesterol concentration, $P = 0.01$ for the comparison of the HDL cholesterol concentration, $P = 0.04$ for the comparison of the concentration of large HDL particles, and $P = 0.02$ for the comparison of the size of HDL particles.

Reproducibility of Findings with the Use of Density-Gradient Ultracentrifugation

Because of the relative novelty of the various measurement techniques for the analysis of lipoprotein subfractions, we thought it important to confirm our findings using a complementary technique. We tested the same hypotheses in 40 subjects (20 in the high-amount–high-intensity group and 20 in the control group) using density-gradient ultracentrifugation combined with direct spectrophotometric measurement of cholesterol in all lipoprotein subfractions.²² The results of the analyses and the conclusions regarding the changes in lipoprotein measurements were similar with the two techniques (data not shown).

DISCUSSION

Our study compared the effects of two different amounts and intensities of exercise training on lipo-

TABLE 2. THE EFFECTS OF THE AMOUNT AND INTENSITY OF EXERCISE ON PLASMA LIPOPROTEINS AS MEASURED BY NUCLEAR MAGNETIC SPECTROSCOPY.*

| VARIABLE | CONTROL GROUP (N = 26) | | LOW-AMOUNT-MODERATE-INTENSITY GROUP (N = 19) | | LOW-AMOUNT-HIGH-INTENSITY GROUP (N = 17) | | HIGH-AMOUNT-HIGH-INTENSITY GROUP (N = 22) | |
|---|---------------------------|--------------|---|--------------|---|--------------|--|--------------|
| | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY |
| Cholesterol (mg/dl) | 205.7±6.9 | 208.3±6.6 | 193.2±5.7 | 194.1±6.5 | 202.3±7.6 | 206.4±5.9 | 202.7±6.4 | 203.1±6.2 |
| LDL cholesterol (mg/dl) | 135.8±4.9 | 138.2±5.1 | 121.6±4.4 | 125.3±5.1 | 131.6±6.7 | 135.2±4.7 | 130.1±5.2 | 128.2±5.2 |
| HDL cholesterol (mg/dl) | 42.7±2.7 | 42.1±2.2 | 40.3±2.2 | 41.0±2.6 | 46.6±3.7 | 46.9±3.4 | 44.3±2.9 | 48.6±3.3 |
| Triglycerides (mg/dl) | 132.1±11.0 | 155.8±14.9 | 196.8±30.5† | 145.2±16.0 | 130.2±14.2 | 117.1±14.2 | 166.9±19.6 | 138.5±13.4 |
| LDL particles (nmol/liter) | 1493±69 | 1610±93 | 1402±58 | 1445±70 | 1400±99 | 1419±84 | 1456±86 | 1391±83 |
| Small LDL particles (mg/dl of cholesterol) | 23.8±7.0 | 37.9±10.2 | 34.5±10.2 | 37.9±10.8 | 20.3±9.9 | 21.7±10.5 | 34.2±9.5 | 27.1±9.5 |
| Size of LDL particles (nm) | 20.9±0.2 | 20.7±0.16 | 20.6±0.2 | 20.6±0.2 | 21.1±0.2 | 21.2±0.2 | 20.8±0.2 | 21.0±0.2 |
| Large VLDL particles (mg/dl of triglycerides) | 25.6±5.4 | 37.6±8.6 | 87.7±27.9‡ | 42.1±11.1 | 32.5±8.5 | 18.2±6.5 | 55.6±14.0 | 36.0±8.6 |
| Size of VLDL particles (nm) | 44.7±1.5 | 49.3±1.9 | 56.8±4.5§ | 49.2±2.5 | 47.8±2.6 | 43.2±2.2 | 49.1±2.4 | 48.1±2.1 |
| Large HDL particles (mg/dl of cholesterol) | 23.4±2.9 | 23.3±2.4 | 22.2±2.5 | 22.4±2.6 | 27.6±4.2 | 28.0±3.8 | 25.1±3.3 | 29.9±3.5 |
| Size of HDL particles (nm) | 8.74±0.09 | 8.69±0.07 | 8.71±0.07 | 8.71±0.08 | 8.92±0.14 | 8.95±0.13 | 8.77±0.09 | 8.89±0.09 |
| IDL cholesterol (mg/dl) | 3.67±1.31 | 3.45±1.11 | 4.24±1.50 | 3.02±1.11 | 3.77±1.25 | 2.01±0.96 | 6.27±1.49 | 3.60±0.97 |

*Plus-minus values are means ±SE. LDL denotes low-density lipoprotein, HDL high-density lipoprotein, VLDL very-low-density lipoprotein, and IDL intermediate-density lipoprotein. 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=0.02 for the comparison with the control group at base line.

‡P=0.004 for the comparison with the control group at base line.

§P=0.002 for the comparison with the control group at base line.

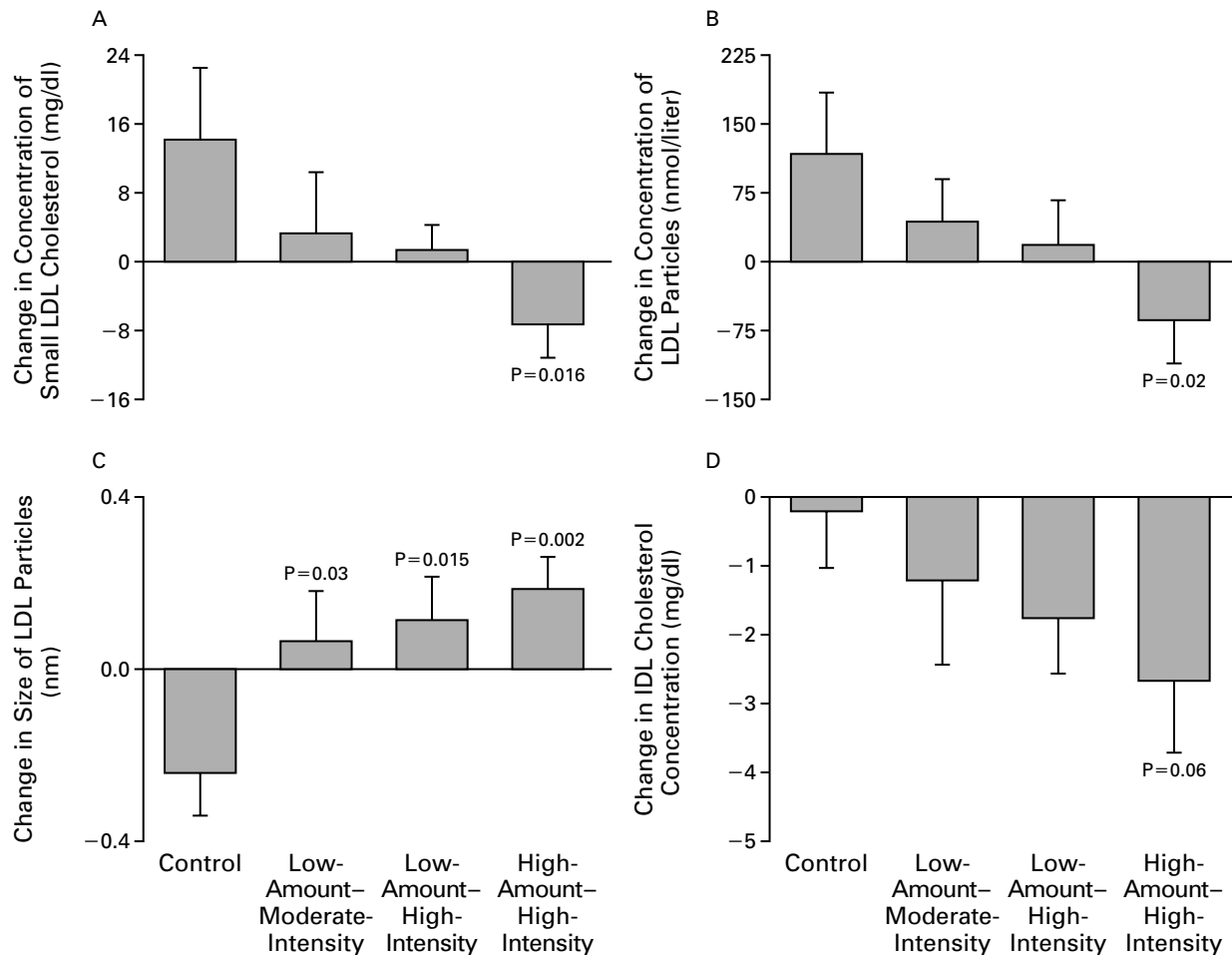


Figure 1. Comparison of the Effects of Three Different Exercise Programs with Those in a Control Group on Mean Changes in the Concentration of Small Low-Density Lipoprotein (LDL) Cholesterol (Panel A), the Concentration of LDL Particles (Panel B), the Average Size of LDL Particles (Panel C), and the Concentration of Intermediate-Density Lipoprotein (IDL) Cholesterol (Panel D).

Subjects in the control group maintained their normal diet and level of physical activity for six months. In the exercise groups, the amount and intensity of exercise were gradually increased to the prescribed level over the course of one to three months, after which exercise was maintained at the prescribed level for six months. Low-amount-moderate-intensity exercise represents the caloric equivalent of walking approximately 12 mi per week at 40 to 55 percent of peak oxygen consumption; low-amount-high-intensity exercise represents the same amount of exercise at 65 to 80 percent of peak oxygen consumption. High-amount-high-intensity exercise represents the caloric equivalent of jogging approximately 20 mi per week at 65 to 80 percent of oxygen consumption. Values shown represent means of individual change scores. I bars represent the standard errors. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

proteins in a prospective, randomized, controlled manner. The data show a clear effect of the amount of exercise on lipoproteins and lipoprotein subfractions; they also show that a relatively high amount of regular exercise — even in the absence of clinically significant weight loss — can significantly improve the overall lipoprotein profile. In particular, the data reveal that exercise at a caloric equivalent of 17 to 18 mi (27.2 to 28.8 km) per week and an intensity equivalent to that of jogging at a moderate pace significantly decreased the concentrations of small LDL and LDL particles

and increased the average size of LDL particles, without changing the plasma LDL cholesterol concentration. This amount of exercise also increased the total HDL concentration, the concentration of large HDL particles, and the average size of HDL particles and decreased the concentrations of triglycerides and total VLDL triglycerides with decreases in the IDL concentration, the concentration of large VLDL particles, and the average size of VLDL particles that were at the margin of statistical significance ($P < 0.07$). These findings were confirmed and strengthened in a parallel

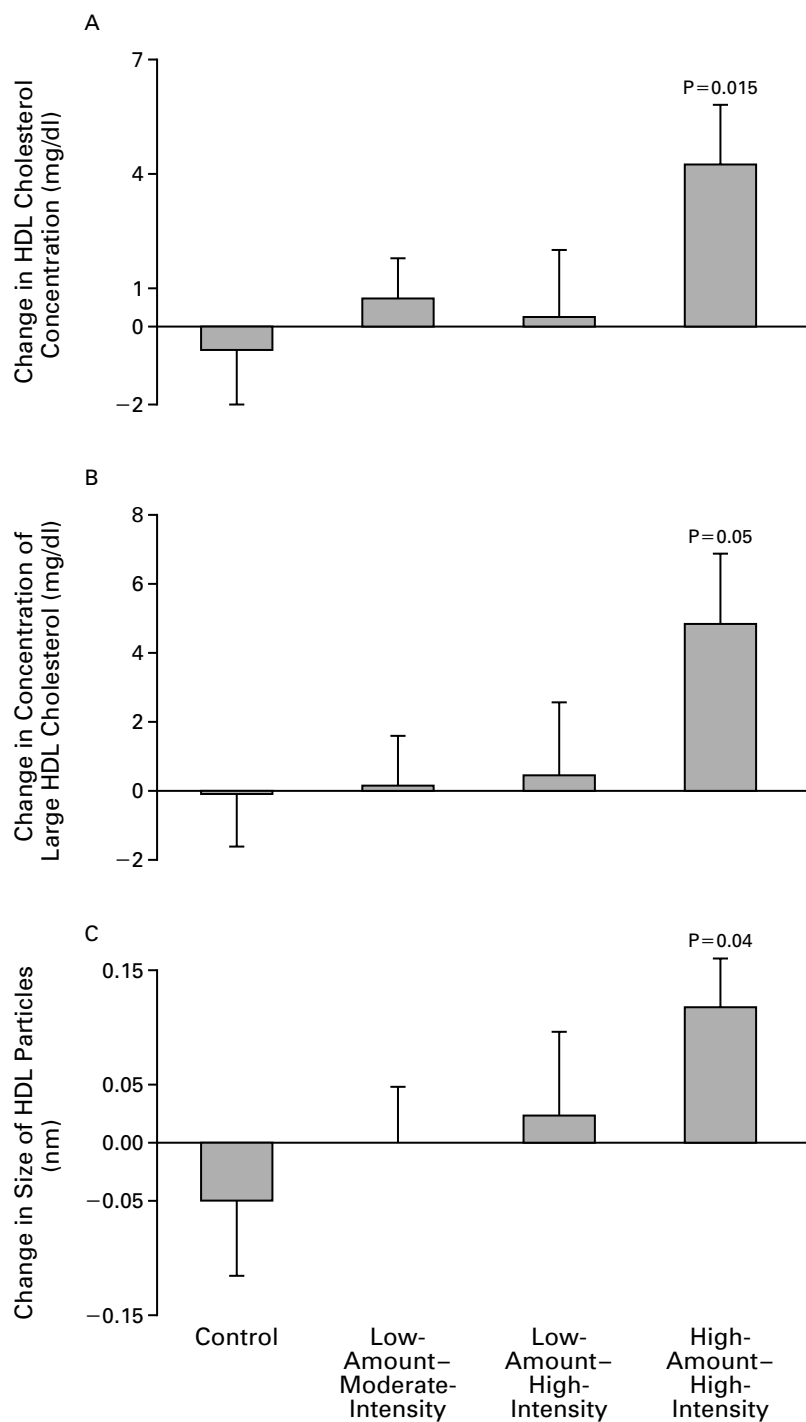


Figure 2. Comparison of the Effects of Three Different Exercise Programs with Those in a Control Group on Mean Changes in Total High-Density Lipoprotein (HDL) Cholesterol Concentration (Panel A), Concentration of Large HDL Cholesterol (Panel B), and Average Size of HDL Particles (Panel C). I bars represent the standard errors. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.

TABLE 3. EFFECTS OF THE AMOUNT AND INTENSITY OF EXERCISE ON LIPIDS, LIPOPROTEINS, AND LIPOPROTEIN SUBFRACTIONS.*

| VARIABLE | EFFECT OF AMOUNT OF EXERCISE | EFFECT OF INTENSITY OF EXERCISE |
|---------------------------------------|----------------------------------|---|
| | | rankings |
| Concentration of small LDL particles | High amount, low amount, control | High intensity, moderate intensity, control |
| Concentration of LDL particles | High amount, low amount, control | High intensity, moderate intensity, control |
| Size of LDL particles | High amount, low amount, control | High intensity, moderate intensity, control |
| IDL concentration | High amount, low amount, control | High intensity, moderate intensity, control |
| Concentration of large HDL particles | High amount, low amount, control | High intensity, moderate intensity, control |
| Size of HDL particles | High amount, low amount, control | High intensity, moderate intensity, control |
| HDL cholesterol concentration | High amount, low amount, control | Moderate intensity, high intensity, control |
| Concentration of large VLDL particles | High amount, low amount, control | Moderate intensity, high intensity, control |
| Size of VLDL particles | Low amount, high amount, control | Moderate intensity, high intensity, control |
| Total triglyceride concentration | High amount, low amount, control | Moderate intensity, high intensity, control |
| VLDL triglyceride concentration | High amount, low amount, control | Moderate intensity, high intensity, control |

*To test for the effect of the amount of exercise, the high-amount–high-intensity, low-amount–high-intensity, and control groups were ranked; the group with the best improvement score is listed first, and the group with the worst score is listed last. The consistency with which the high amount of exercise was ranked first (10 of 11 variables) and with which the control condition ranked last (11 of 11 variables) emphasizes the clear effect of the amount of exercise. To test for an effect of the intensity of exercise, the low-amount–high-intensity, low-amount–moderate-intensity, and control groups were ranked in the same manner. The high-intensity group ranked first in 6 of 11 variables, and the moderate-intensity group ranked first in 5 of 11 variables. We interpret this fairly equal distribution to indicate that there is no clear effect of the intensity of exercise.

intention-to-treat analysis. None of these improvements, except for those in HDL cholesterol and triglycerides, would have been detected by the standard lipid panel. These data refute the general conclusion, based on results from the standard lipid panel and on studies in which moderate amounts of exercise (similar to that in the low-amount groups in our study) were used, that exercise has only limited effects on lipids and lipoproteins.⁶

The second major finding is that the amount of exercise appears to make a greater difference than the intensity of exercise on plasma lipoprotein concentrations. Our data agree with those of Duncan et al.,²³ in which three walking groups (strollers, brisk walkers, and aerobic walkers) exercised the same amount (approximately 13 mi [20.8 km] per week) for 24 weeks. The strollers and aerobic walkers had improvements of 6 percent and brisk walkers an improvement of 4 percent in the HDL cholesterol concentration. Several

studies have shown that low-intensity exercise can result in improvements in lipoproteins.^{23–26} Our data, taken together with those of others, suggest that any effect on lipids of the intensity of exercise is small as compared with that of the amount of exercise. A high-amount–moderate-intensity group was not included in our study because of the very large weekly time commitment that would have been required (up to eight hours for subjects with a low level of fitness). Thus, we cannot exclude the possibility that the level of intensity would have an effect in subjects with higher amounts of exercise.

Cross-sectional studies have reported that runners have smaller amounts of atherogenic small LDL particles than do controls who do not exercise.^{27,28} However, in those studies, the percentage of body fat was significantly higher among the sedentary subjects, potentially confounding the results. In an exercise study, Williams et al.²⁹ reported no difference between subjects randomly assigned to exercise and controls in any changes in LDL or VLDL subfractions. These findings were most likely due to the small average amount of exercise of only about 8 mi (12.8 km) per week. When the investigators examined the correlation between the concentration of small LDL particles and the distance run by subjects within the running group, they found a significant, albeit small, inverse relation. It is important to note that weight loss was permitted in that study, and the investigators ascribed most of the change to weight loss. Several studies have reported significant effects of exercise on lipoproteins. However, in those studies, exercise induced larger weight losses than those seen in our study, and the effect was generally attributed to or correlated with weight loss.^{29–33} In our study, we were able to minimize greatly, although not to eliminate completely, weight differences and weight loss as confounding factors.

Some additional conclusions are warranted. First, although the lower amount of exercise resulted in fewer significant improvements, this amount of exercise was able to limit or prevent in the low-amount groups much of the weight gain and consequent worsening of the overall lipoprotein profile that was observed in the control group. Second, although the two high-intensity groups had very similar increases in fitness (as measured by peak oxygen consumption), only the high-amount group had extensive improvements in the overall lipoprotein profile. Similarly, the same low amount of weekly exercise had very different effects on fitness in the high-intensity group and the moderate-intensity group but had similar effects on the lipoprotein profile in the two groups. Therefore, it would appear that it is the amount of activity — and not necessarily the change in fitness — that is important for the improvement of the lipoprotein profile with exercise programs.

TABLE 4. INTENTION-TO-TREAT ANALYSIS OF EFFECTS OF THE AMOUNT AND INTENSITY OF EXERCISE ON PLASMA LIPOPROTEINS AS MEASURED BY NUCLEAR MAGNETIC SPECTROSCOPY.*

| VARIABLE | CONTROL GROUP (N=26) | | LOW-AMOUNT-MODERATE-INTENSITY GROUP (N=26) | | LOW-AMOUNT-HIGH-INTENSITY GROUP (N=18) | | HIGH-AMOUNT-HIGH-INTENSITY GROUP (N=31) | | INTENTION-TO-TREAT ANALYSIS (N=101) | MAIN ANALYSIS (N=84) |
|---|----------------------|--------------|--|--------------|--|--------------|---|--------------|-------------------------------------|----------------------|
| | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY | BASE LINE | END OF STUDY | | |
| Cholesterol (mg/dl) | 205.7±6.9 | 208.3±6.6 | 194.0±4.8 | 197.9±5.4 | 205.5±7.8 | 208.1±5.8 | 200.1±5.9 | 199.1±5.8 | NS | NS |
| LDL cholesterol (mg/dl) | 135.8±4.9 | 138.2±5.1 | 122.7±4.0 | 127.8±4.1 | 133.6±6.6 | 135.7±4.5 | 130.1±4.8 | 126.5±4.9 | NS | NS |
| HDL cholesterol (mg/dl) | 42.7±2.7 | 42.1±2.2 | 42.0±1.9 | 43.1±2.5 | 48.1±3.8 | 48.9±3.7 | 42.1±2.3 | 45.9±2.6 | 0.01 | 0.015 |
| Triglycerides (mg/dl) | 132.1±11.0 | 155.8±14.9 | 188.0±23.2‡ | 137.6±12.2 | 128.0±13.6 | 114.7±13.6 | 158.0±15.0 | 138.0±10.8 | 0.005 | 0.006 |
| LDL particles (nmol/liter) | 1493±69 | 1610±93 | 1378±53 | 1437±58 | 1405±93 | 1411±79 | 1502±80 | 1406±75 | 0.002 | 0.02 |
| Small LDL particles (mg/dl of cholesterol) | 23.8±7.0 | 37.9±10.2 | 28.5±7.9 | 33.2±8.4 | 19.2±9.4 | 20.5±10.0 | 40.0±8.2 | 30.2±8.2 | 0.002 | 0.016 |
| Size of LDL particles (nm) | 20.9±0.2 | 20.7±0.2 | 20.7±0.2 | 20.8±0.2 | 21.2±0.2 | 21.3±0.2 | 20.6±0.2 | 20.9±0.2 | <0.001 | 0.002 |
| Large VLDL particles (mg/dl of triglycerides) | 25.6±5.4 | 37.6±8.6 | 80.4±20.8§ | 38.4±8.7 | 30.7±8.2 | 17.2±6.2 | 50.8±10.7 | 36.3±7.1 | 0.05 | 0.05 |
| Size of VLDL particles (nm) | 44.7±1.5 | 49.3±1.9 | 55.9±3.5¶ | 49.4±2.2 | 47.4±2.5 | 43.3±2.1 | 49.1±2.0 | 48.0±1.8 | 0.03 | 0.06 |
| Large HDL particles (mg/dl of cholesterol) | 23.4±2.9 | 23.3±2.4 | 24.0±2.3 | 24.9±2.6 | 28.8±4.2 | 29.7±4.0 | 22.7±2.6 | 27.6±2.7 | 0.04 | 0.05 |
| Size of HDL particles (nm) | 8.7±0.09 | 8.7±0.07 | 8.8±0.07 | 8.8±0.09 | 9.0±0.14 | 9.0±0.13 | 8.7±0.08 | 8.9±0.07 | 0.02 | 0.04 |
| IDL cholesterol (mg/dl) | 3.6±1.3 | 3.5±1.1 | 5.0±1.3 | 3.2±1.1 | 3.6±1.2 | 1.9±0.9 | 6.4±1.3 | 3.2±0.9 | 0.02 | 0.06 |

*Plus-minus values are means ±SE. Data are for the 101 subjects with complete lipid data. NS denotes not significant, LDL low-density lipoprotein, HDL high-density lipoprotein, VLDL very-low-density lipoprotein, and IDL intermediate-density lipoprotein. 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 values are for the comparison between the change in the high-intensity group and the change in the control group.

‡P=0.02 for the comparison with the control group at base line.

§P=0.004 for the comparison with the control group at base line.

¶P=0.002 for the comparison with the control group at base line.

In conclusion, our study demonstrates that regular exercise with minimal weight change has broad beneficial effects on the lipoprotein profile. A clear, biologically consistent association emerged between the amount of exercise and the degree of improvement in the lipoprotein profile, with the higher amount of exercise (equivalent to 17 to 18 mi of jogging at a moderate pace per week) having a much greater beneficial effect on lipids and lipoproteins than the lower amount of exercise (equivalent to jogging or walking approximately 11 mi per week). The lower amount of exercise prevented the weight gain seen in the controls and was clearly more beneficial for the lipoprotein profile than was a sedentary lifestyle. The greater amount of exercise was approximately that which, according to the initial results, provided the maximal benefit in preventing cardiovascular events and death from any cause among subjects in the Harvard Alumni Study.³⁴ The extensive improvements achieved in the high-amount–high-intensity group were related to the amount of physical activity and did not appear to be related to changes in the level of fitness. Finally, the intensity of exercise was less important, at least in the case of the lower amount of exercise studied, than the amount of exercise in terms of lipoprotein responses.

Supported by a grant (HL-57354) from the National Institutes of Health. Dr. Otvos reports being an employee, officer, and stockholder of Liposcience.

Dr. Kulkarni reports being an employee of Atherotech and having options for the purchase of stock. He also receives royalties as an inventor of the Vertical Auto Profile technology.

REFERENCES

- Leon A, Connett J, Jacobs D Jr, Raurama R. Leisure-time physical activity levels and risk of coronary heart disease and death: the Multiple Risk Factor Intervention Trial. *JAMA* 1987;258:2388-95.
- Paffenbarger RS Jr, Hyde RT, Wing AL, Hsieh C. Physical activity, all-cause mortality, and longevity of college alumni. *N Engl J Med* 1986;314:605-13.
- Paffenbarger RS Jr, Hyde RT, Wing AL, Lee I-M, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. *N Engl J Med* 1993;328:538-45.
- Blair S, Kohl HW III, Paffenbarger RS Jr, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality: a prospective study of healthy men and women. *JAMA* 1989;262:2395-401.
- Blair SN, Kohl HW III, Barlow CE, Paffenbarger RS Jr, Gibbons LW, Macera CA. Changes in physical fitness and all-cause mortality: a prospective study of healthy and unhealthy men. *JAMA* 1995;273:1093-8.
- Leon AS, Sanchez OA. Response of blood lipids to exercise training alone or combined with dietary intervention. *Med Sci Sports Exerc* 2001;33:Suppl:S502-S515.
- Durstine JL, Haskell WL. Effects of exercise training on plasma lipids and lipoproteins. *Exer Sport Sci Rev* 1994;22:477-521.
- Sniderman AD, Pedersen T, Kjekshus J. Putting low-density lipoproteins at center stage in atherogenesis. *Am J Cardiol* 1997;79:64-7.
- Vakkilainen J, Makimattila S, Seppala-Lindroos A, et al. Endothelial dysfunction in men with small LDL particles. *Circulation* 2000;102:716-21.
- Zilversmit DB. Atherogenic nature of triglycerides, postprandial lipemia, and triglyceride-rich remnant lipoproteins. *Clin Chem* 1995;41:153-8.
- Cheung MC, Brown BG, Wolf AC, Albers JJ. Altered particle size distribution of apolipoprotein A-I-containing lipoproteins in subjects with coronary artery disease. *J Lipid Res* 1991;32:383-94.
- Kamigaki AS, Siscovick DS, Schwartz SM, et al. Low density lipoprotein particle size and risk of early-onset myocardial infarction in women. *Am J Epidemiol* 2001;153:939-45.
- Kwiterovich PO Jr, Coresh J, Bachorik PS. Prevalence of hyperapobetalipoproteinemia and other lipoprotein phenotypes in men (aged ≤ 50 years) and women (≤ 60 years) with coronary artery disease. *Am J Cardiol* 1993;71:631-9.
- Lamarche B, Despres JP, Moorjani S, Cantin B, Dagenais GR, Lupien P. Prevalence of dyslipidemic phenotypes in ischemic heart disease (prospective results from the Quebec Cardiovascular Study). *Am J Cardiol* 1995;75:1189-95.
- Kwiterovich PO Jr. HyperapoB: a pleiotropic phenotype characterized by dense low-density lipoproteins and associated with coronary artery disease. *Clin Chem* 1988;34:B71-B77.
- Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men: prospective results from the Quebec Cardiovascular Study. *Circulation* 1997;95:69-75.
- Pascot A, Lemieux I, Prud'homme D, et al. Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. *J Lipid Res* 2001;42:2007-14.
- Kraus WE, Torgan CE, Duscha BD, et al. Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE). *Med Sci Sports Exerc* 2001;33:1774-84.
- Passmore R, Durnin JVGA. Human energy expenditure. *Physiol Rev* 1955;35:801-40.
- Otvos J, Jeyarajah E, Bennett D. Quantification of plasma lipoproteins by proton nuclear magnetic resonance spectroscopy. *Clin Chem* 1991;37:377-86.
- Otvos J, Jeyarajah E, Bennett D, Kraus R. Development of a proton nuclear magnetic resonance spectroscopic method for determining plasma lipoprotein concentrations and subspecies distributions from a single, rapid measurement. *Clin Chem* 1992;38:1632-8.
- Kulkarni KR, Garber DW, Marcovina SM, Segrest JP. Quantification of cholesterol in all lipoprotein classes by the VAP-II method. *J Lipid Res* 1994;35:159-68.
- Duncan JJ, Gordon NF, Scott CB. Women walking for health and fitness: how much is enough? *JAMA* 1991;266:3295-9.
- Crouse SF, O'Brien BC, Grandjean PW, et al. Training intensity, blood lipids, and apolipoproteins in men with high cholesterol. *J Appl Physiol* 1997;82:270-7.
- King AC, Haskell WL, Young DR, Oka RK, Stefanick ML. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women age 50 to 65 years. *Circulation* 1995;91:2596-604.
- Sunami Y, Motoyama M, Kinoshita F, et al. Effects of low-intensity aerobic training on the high-density lipoprotein cholesterol concentration in healthy elderly subjects. *Metabolism* 1999;48:984-8.
- Halle M, Berg A, Baumstark MW, Keul J. Association of physical fitness with LDL and HDL subfractions in young healthy men. *Int J Sports Med* 1999;20:464-9.
- Williams PT, Krauss RM, Wood PD, Lindgren FT, Giotas C, Vranizan KM. Lipoprotein subfractions of runners and sedentary men. *Metabolism* 1986;35:45-52.
- Williams PT, Krauss RM, Vranizan KM, Albers JJ, Terry RB, Wood PD. Effects of exercise-induced weight loss on low density lipoprotein subfractions in healthy men. *Arteriosclerosis* 1989;9:623-32.
- Williams PT, Krauss RM, Vranizan KM, Albers JJ, Wood PD. Effects of weight-loss by exercise and by diet on apolipoproteins A-I and A-II and the particle-size distribution of high-density lipoproteins in men. *Metabolism* 1992;41:441-9.
- Wood PD, Stefanick ML, Dreon DM, et al. Changes in plasma lipids and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *N Engl J Med* 1988;319:1173-9.
- Williams PT, Krauss RM, Vranizan KM, Wood PD. Changes in lipoprotein subfractions during diet-induced and exercise-induced weight loss in moderately overweight men. *Circulation* 1990;81:1293-304.
- Williams PT, Wood PD, Haskell WL, Vranizan KM. The effects of running mileage and duration on plasma lipoprotein levels. *JAMA* 1982;247:2674-9.
- Paffenbarger RS Jr, Wing AL, Hyde RT. Physical activity as an index of heart attack risk in college alumni. *Am J Epidemiol* 1978;108:161-75.

Copyright © 2002 Massachusetts Medical Society.