

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL AND OTHER RISK FACTORS FOR CORONARY HEART DISEASE IN FEMALE RUNNERS

PAUL T. WILLIAMS, PH.D.

Abstract *Background.* Official guidelines from the Centers for Disease Control and Prevention assert that the majority of health benefits from physical activity are obtained by walking 2 miles (3.2 km) briskly most days of the week (the energy equivalent of running 8 to 12 km per week). The objective of our study was to examine the dose-response relation in women between risk factors for coronary heart disease, particularly the concentration of high-density lipoprotein (HDL) cholesterol, and vigorous exercise at levels that exceed the official guidelines.

Methods. The number of kilometers run per week reported by 1837 female recreational runners in a national cross-sectional survey was compared with medical data provided by the women's physicians.

Results. In these cross-sectional data, plasma HDL cholesterol concentrations were higher by an average (\pm SE) of 0.133 ± 0.020 mg per deciliter (0.003 ± 0.0005 mmol per liter) for every additional kilometer run per week, an amount nearly identical with that previously reported for men (0.136 ± 0.006 mg per deciliter [0.004 ± 0.0002

mmol per liter] per kilometer per week). Among women who ran less than 48 km per week, mean plasma HDL concentrations were significantly higher with each 16-km increment in distance. Women who ran more than 64 km per week had significantly higher mean concentrations of HDL cholesterol than did women who ran less than 48 km per week. They were also significantly more likely to have HDL cholesterol concentrations greater than 100, 90, or 80 mg per deciliter (2.6, 2.3, or 2.1 mmol per liter) than were women running less than 64 km per week. HDL cholesterol concentrations increased significantly in relation to the number of kilometers run per week in premenopausal women who were not using oral contraceptives and in postmenopausal women, whether they were receiving estrogen-replacement therapy or not.

Conclusions. Substantial increases in HDL cholesterol concentrations were found in women who exercised at levels exceeding current guidelines; higher HDL cholesterol concentrations could provide added health benefits to these women. (N Engl J Med 1996;334:1298-303.)

©1996, Massachusetts Medical Society.

RECENT guidelines from the Centers for Disease Control and Prevention (CDC)¹ assert that the majority of health benefits from physical activity can be achieved by walking 2 miles (3.2 km) briskly most days of the week (the energy equivalent of running 8 to 12 km per week²). The guidelines also assert that the benefit of increasing one's level of physical activity is 12 times greater in sedentary than in active people.³ These recommendations were directed at the 24 percent of adult Americans who are completely sedentary and the 54 percent whose level of physical activity is inadequate.^{4,5} However, data collected as part of the National Runners' Health Study suggest that in men there are substantial additional reductions in risk factors for coronary heart disease if their level of physical activity exceeds the recommended guidelines.⁶ Specifically, the beneficial effects of exercise (i.e., higher concentrations of high-density lipoprotein [HDL] cholesterol and lower adiposity, triglyceride concentrations, ratio of total cholesterol to HDL cholesterol, and estimated 10-year risk of coronary heart disease) appear to increase with distances run of up to at least 80 km per week.

Whether these findings in men also apply to women is unknown. Heart disease is less likely to develop in women than in men,⁷ and women have different levels of risk factors for heart disease⁸ and possibly different physiologic responses to physical activity.⁹⁻¹¹ Physical

activity appears to reduce the risk of coronary heart disease in women as well as in men, however.^{12,13} The reduction may be due in part to higher levels of HDL cholesterol. In women as in men, plasma HDL cholesterol concentrations appear to increase with physical activity¹⁴⁻²³ and to prevent coronary heart disease.²⁴⁻²⁶ However, little is known about the dose-response relation between the level of exercise and HDL cholesterol in women or about the way menstrual status and hormone use may affect this relation.^{9,10,27,28} We therefore examined the dose-response relation between the reported distance run per week and risk factors for coronary heart disease in 1837 female runners who participated in the National Runners' Health Study. The specific aim of this study was to determine whether health benefits accrue in women at levels of exercise that exceed current minimal guidelines.

METHODS

Using a two-page questionnaire, distributed nationally at races and to subscribers of a major running magazine (*Runner's World*, Kodale Press, Emmaus, Pa.), we solicited information on demographic characteristics (age, race, and education); running history (age when the participant began running at least 12 miles [19.2 km] per week, average weekly distance run and number of marathons run over the preceding five years, best marathon and 10-km running times); weight history (highest and current weight; weight when the participant started running; lowest weight as a runner; circumferences of the chest, waist, and hips; and bra-cup size); menstrual history (whether currently having periods and age at menarche); hormone use (birth-control pills, postmenopausal estrogen replacement, or progesterone); diet (whether vegetarian; weekly intake of alcohol, red meat, fish, fruit, vitamin C, vitamin E, and aspirin); current and past cigarette use; history of heart attack and cancer; and medications taken to treat high blood pressure, thyroid conditions, high cholesterol levels, or diabetes. The questionnaire also requested permission to obtain the participants' height, weight, plasma cholesterol and triglyceride concentrations, blood pres-

From the Life Sciences Division, Lawrence Berkeley National Laboratory, Bldg. 934, Berkeley, CA 94720, where reprint requests should be addressed to Dr. Williams.

Supported in part by grants (HL-45652 and HL-55640) from the National Heart, Lung, and Blood Institute and a grant (DE-AC03-76SF00098) from the Department of Energy at the University of California.

sure, and heart rate at rest from their physicians. Consent to participate in the study was obtained from all study subjects, and the study design was approved by the committee for the protection of human subjects.

The average distance run per week was computed by averaging the reported weekly distance over the preceding five years. The amount of alcohol consumed per week was calculated by multiplying the number of various drinks consumed by 0.48 oz (14 ml) per 12-oz (350-ml) bottle of beer, 0.48 oz per 4-oz (120-ml) glass of wine, and 0.60 oz (18 ml) per drink of hard liquor.²⁹ The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. Bra-cup sizes were coded on a 4-point scale: 1 (A cup), 2 (B cup), 3 (C cup), or 4 (D cup or larger). Bra size was included because it is a component of chest circumference that has been found to be related to the HDL cholesterol concentration.³⁰ Data on HDL cholesterol were obtained from the medical records of 2667 female runners. We excluded 151 runners who had histories of cancer or heart attacks, 52 who smoked, 400 who followed vegetarian diets, and 227 who were taking medications that could potentially affect the concentrations of plasma lipoproteins. This left 1837 nonvegetarian, nonsmoking runners who had no history of heart disease or cancer and who were not using medications that might affect lipoprotein concentrations.

Multiple regression analyses were used to test for overall linear relations between the distance run and risk-factor levels and to assess the significance of these relations after adjustment for other variables.³¹ Two-sample t-tests were used to compare mean risk-factor levels among the distance categories.³¹ We tested linear trends for proportions using the estimated trends and standard errors for linear contrasts among the five distance categories.³¹

RESULTS

Table 1 shows that women who ran greater weekly distances tended to adopt types of behavior reflecting greater health consciousness: they consumed fewer weekly servings of beef, lamb, or pork and had higher weekly intakes of fruit and vitamin E. Age, education, and intake of fish, alcohol, aspirin, and vitamin C were all unrelated to running distance. As expected, the runners in the longer-distance categories were more likely to have participated in at least one marathon or 10-km race over the preceding five years and to have completed those races more quickly. Longer distances run were also associated with lower heart rates at rest and more years spent running at a level of 12 miles or more per week. There were 447 women (24.3 percent) who reported no longer having menstrual periods, 176 women (9.6 percent) who reported receiving postmenopausal estrogen-replacement therapy, 73 women (4.0 percent) who reported taking progesterone, and 236 women (12.8 percent) who reported using oral contraceptives. Menstrual status and hormone use were unrelated to distance run per week (Table 1).

HDL cholesterol concentrations were found to increase significantly in relation to longer weekly distanc-

es run (mean regression slope [\pm SE]: $\beta = 0.133 \pm 0.020$ mg per deciliter [0.003 ± 0.0005 mmol per liter] for each additional kilometer per week). As Table 2 shows, mean plasma concentrations of HDL cholesterol were significantly higher with each 16-km increment in the weekly running distance up to 48 km run per week and at or above 64 km per week. The higher HDL cholesterol concentration could not be attributed to age; education; menstrual status; intake of alcohol, aspirin, red meat, fish, fruit, or vitamin C or E; or use of progesterone, estrogen, or birth-control pills (i.e., the regression slope was $\beta = 0.128 \pm 0.019$ mg per deciliter [0.003 ± 0.0005 mmol per liter] per kilometer per week after adjustment for these variables). Figure 1 shows that the HDL cholesterol concentration was increased with greater running distances in premenopausal women who were not using oral contraceptives ($\beta = 0.140 \pm 0.024$ mg per deciliter [0.004 ± 0.0006 mmol per liter] per kilometer per week), in postmenopausal women who were not taking estrogen ($\beta = 0.136 \pm 0.040$ mg per deciliter [0.004 ± 0.001 mmol per liter] per kilometer per week), and in postmenopausal women taking estrogen ($\beta = 0.148 \pm 0.066$ mg per deciliter [0.004 ± 0.002 mmol per liter] per kilometer per week) after adjustment for the variables indicated above. Among women using birth-control pills, the regression slope for HDL cholesterol plotted against distance run ($\beta = 0.080 \pm 0.050$ mg per deciliter [0.002 ± 0.001 mmol per liter] per kilometer

Table 1. Relation between Reported Distance Run per Week and Age, Education, Diet, and Running History in 1837 Female Runners.*

VARIABLE	REPORTED DISTANCE RUN PER WEEK (KM)					P VALUE†
	0-15.9 (N = 193)	16-31.9 (N = 651)	32-47.9 (N = 567)	48-63.9 (N = 290)	64-139.0 (N = 136)	
Age (yr)	39.9±9.5	40.8±9.4	40.5±9.6	39.9±10.1	40.0±8.4	0.32
Education (yr)	15.9±2.4	15.9±2.4	16.0±2.4	15.8±2.4	16.1±2.3	0.80
Years of running	6.1±6.0	7.8±5.8	9.8±5.1	10.7±5.3	11.1±4.9	<0.001
Distance run (km/wk)	10.5±4.1	24.0±4.4	39.0±4.7	54.3±4.8	77.3±13.0	<0.001
Menstruating (%)	77.2±3.0	75.7±1.7	76.9±1.8	72.8±2.6	74.3±3.8	0.39
Postmenopausal estrogen therapy (%)	9.8±2.1	9.4±1.1	10.4±1.3	10.0±1.8	5.9±2.0	0.25
Use of birth-control pills (%)	11.4±2.3	12.0±1.3	14.1±1.5	13.1±2.0	13.2±2.9	0.55
Marathon participation						
One or more (%)	6.2±1.7	17.4±1.5	40.7±2.1	59.3±2.9	68.4±4.0	<0.001
Average best time (min)	286.5±76.4	278.1±48.6	251.3±34.7	231.2±32.4	210.4±28.6	<0.001
10-km-race participation						
One or more (%)	48.7±3.6	75.6±1.7	84.0±1.5	90.3±1.7	94.1±2.0	<0.001
Average best time (min)	55.2±8.5	51.9±6.6	48.8±6.2	45.4±6.4	42.1±5.0	<0.001
Resting pulse rate (bpm)	68.9±8.6	66.5±9.7	64.7±10.2	63.3±10.6	60.9±11.1	<0.001
Alcohol intake (oz)	1.6±2.2	1.7±2.5	1.8±2.6	1.8±3.8	2.0±3.1	0.12
Dietary intake (servings/wk)						
Beef, lamb, or pork	2.3±1.8	2.2±2.1	1.8±1.8	1.7±1.8	1.8±2.3	<0.001
Fish	1.2±1.1	1.4±1.2	1.6±1.5	1.4±1.3	1.5±1.4	0.09
Fruit	10.3±6.8	11.3±6.9	11.5±7.2	13.1±8.7	10.8±7.6	0.03
Aspirin intake (tablets/wk)	2.2±3.9	2.0±4.7	2.4±5.0	2.6±6.3	2.2±6.4	0.28
Vitamin C intake (g/wk)	1.5±2.6	1.4±3.1	1.8±3.9	1.8±4.8	1.9±3.5	0.13
Vitamin E intake (IU/wk)	475±1297	499±1180	642±1380	736±1632	662±2167	0.05

*Percentages are shown as means \pm SE. All other plus-minus values are means \pm SD. To convert kilometers to miles, multiply by 0.6214. To convert ounces to milliliters, multiply by 29.574.

†P values are for linear trend.

Table 2. Relation between Reported Distance Run per Week and Measures of Adiposity, Blood Pressure, and Plasma Lipoprotein Concentrations in 1837 Female Runners.*

VARIABLE	REPORTED DISTANCE RUN PER WEEK (KM)					P VALUE†
	0–15.9 (N = 193)	16–31.9 (N = 651)	32–47.9 (N = 567)	48–63.9 (N = 290)	64–139.0 (N = 136)	
HDL cholesterol (mg/dl)	59.2±1.0	62.1±0.6‡	64.2±0.6§	65.9±0.9§	68.8±1.7¶	<0.001
Low-density lipoprotein cholesterol (mg/dl)	109.6±2.1	108.9±1.2	106.0±1.3	106.7±1.9	111.3±3.1	0.46
Triglycerides (mg/dl)	86.4±3.4	81.9±2.9	79.3±1.7	82.8±2.7	79.7±5.1	0.50
Total cholesterol:HDL cholesterol	3.3±0.1	3.2±0.0	3.0±0.0§	3.0±0.0§	3.0±0.1‡	<0.001
Systolic blood pressure (mm Hg)	115.5±1.1	113.7±0.6	111.9±0.6§	111.9±0.9‡	112.2±1.2‡	0.003
Diastolic blood pressure (mm Hg)	73.3±0.7	72.1±0.4	71.1±0.4‡	70.2±0.6§	72.3±0.9	0.03
Body-mass index	22.6±0.3	21.6±0.1‡	21.1±0.1§	20.6±0.1¶	20.1±0.1**	<0.001
Waist circumference (cm)	71.9±0.7	69.6±0.3‡	67.6±0.2§	67.2±0.4§	65.5±0.4**	<0.001
Hip circumference (cm)	94.7±0.6	92.9±0.3‡	91.4±0.2§	89.9±0.4¶	88.4±0.5**	<0.001
Chest circumference (cm)	89.7±0.5	88.6±0.2‡	87.4±0.2§	87.2±0.3§	86.2±0.4¶	<0.001
Bra-cup size††	2.1±0.1	1.9±0.0‡	1.9±0.0‡	1.8±0.1‡	1.7±0.1¶	0.001
Change since starting to run						
Body-mass index	0.5±0.2	0.1±0.1‡	0.0±0.1‡	-0.6±0.1¶	-0.3±0.2§	<0.001
Waist circumference (cm)	0.6±0.6	-0.2±0.3	-0.6±0.2‡	-1.5±0.4¶	-1.3±0.4§	0.002
Hip circumference (cm)	0.2±0.5	-0.4±0.2	-0.6±0.3	-1.7±0.3¶	-1.4±0.4‡	<0.001
Chest circumference (cm)	0.1±0.4	0.0±0.2	0.0±0.2	-0.7±0.3¶	-0.5±0.4	0.02
Bra-cup size††	0.0±0.1	0.0±0.0	-0.1±0.0	-0.1±0.0§	-0.2±0.1§	0.001

*Plus-minus values are means ±SE. To convert kilometers to miles, multiply by 0.6214. 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 linear trend.

‡P<0.05 for the comparison with the 0-to-15.9-km category.

§P<0.05 for the comparisons with the 0-to-15.9-km and 16-to-31.9-km categories.

¶P<0.05 for the comparisons with the 0-to-15.9-km, 16-to-31.9-km, and 32-to-47.9-km categories.

||Body-mass index is calculated as the weight in kilograms divided by the square of the height in meters.

**P<0.05 for the comparisons with all distance categories below 64 km.

††See the Methods section for the 4-point scale for bra-cup size.

per week) was neither significantly greater than zero ($P=0.11$) nor significantly less than the regression slope for women not using birth-control pills ($P=0.27$).

Increased weekly running distance was associated with significant increases in the percentage of women with HDL cholesterol concentrations above 50, 60, 70, 80, 90, or 100 mg per deciliter (1.3, 1.6, 1.8, 2.1, 2.3, or 2.6 mmol per liter) (Fig. 2). Women who ran at least 64 km per week were significantly more likely ($P<0.02$) to have high concentrations of HDL cholesterol (i.e., more than 100, 90, or 80 mg per deciliter) than women running shorter distances. The few women who had low HDL cholesterol concentrations (4.5 percent below 40 mg per deciliter [1.0 mmol per liter] and 1.3 percent below 35 mg per deciliter [0.9 mmol per liter]) were distributed randomly among the weekly-distance categories.

As Table 2 shows, other cardiovascular risk factors were significantly reduced in association with longer running distances, including the ratio of total cholesterol to HDL cholesterol ($\beta=-0.005\pm0.001$ per kilometer per week), systolic blood pressure ($\beta=-0.06\pm0.02$ mm Hg per kilometer per week), and diastolic blood pressure ($\beta=-0.028\pm0.013$ mm Hg per kilometer per week). All three variables remained significantly related to distance after we adjusted for the women's age, education, menstrual status, hormone use, and diet. Levels of neither low-density lipoprotein cholesterol ($\beta=-0.03\pm0.04$ mg per deciliter [0.0008 ± 0.001 mmol per liter] per kilometer per week) nor triglycerides ($\beta=-0.049\pm0.074$ mg

per deciliter [0.0006 ± 0.0008 mmol per liter] per kilometer per week) showed any relation to distance run by the women. Adiposity, as measured by the body-mass index, decreased significantly with longer distance ($\beta=-0.036\pm0.003$ per kilometer per week); the circumferences of the waist ($\beta=-0.091\pm0.009$ cm per kilometer per week), hip ($\beta=-0.097\pm0.009$ cm per kilometer per week), and chest ($\beta=-0.052\pm0.007$ cm per kilometer per week); and bra cup ($\beta=-0.005\pm0.001$ cup size per kilometer per week).

The higher HDL cholesterol concentrations and the lower values for pulse rate, blood pressure, body-mass index, and body circumferences in the women who ran longer distances could not be attributed to a choice by the initially leaner women to run farther (i.e., self-selection based on adiposity). As part of the questionnaire, runners reported their initial weights and body-circumference values when they started running. We used these to calculate the change in runners' body-mass-index and body-circumference values since they started to run (Table 2). Longer weekly distance was associated with greater reductions in body-mass index ($\beta=-0.014\pm0.003$ per kilometer per week) and the circumferences of the waist ($\beta=-0.031\pm0.008$ cm per kilometer per week), hip ($\beta=-0.030\pm0.008$ cm per kilometer per week), and chest ($\beta=-0.014\pm0.006$ cm per kilometer per week) since running was begun. When adjusted for the initial body-mass index, running greater weekly distances continued to be associated with an

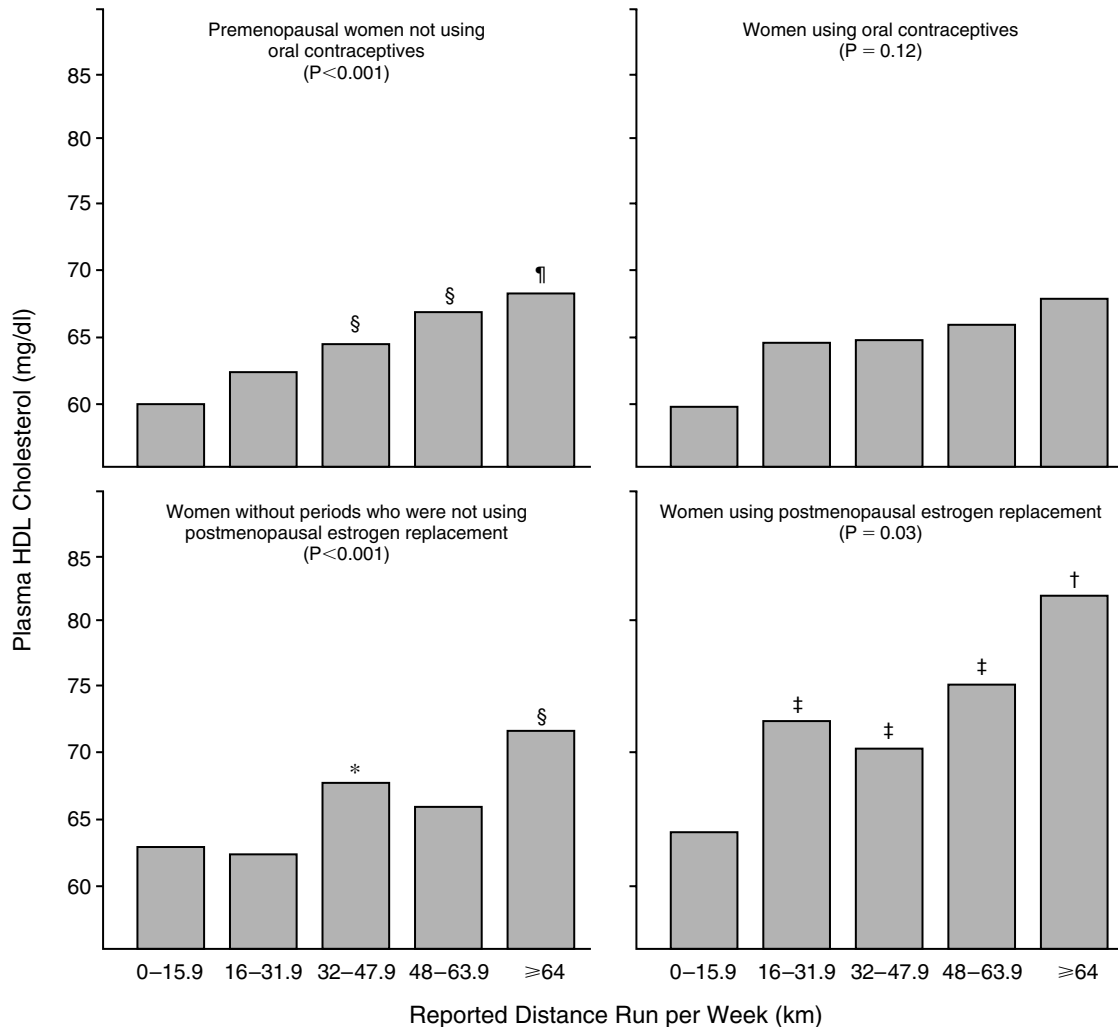


Figure 1. Plasma HDL Cholesterol Concentrations According to Weekly Distance Run.

Menstrual periods were reported by 1390 women; the absence of periods was reported by 447. A total of 236 women reported using oral contraceptives, and 176 reported using postmenopausal estrogen-replacement therapy. The P values shown in the figure are for the regression slope for HDL cholesterol plotted against distance run, with adjustment for age, education, progesterone use, and intake of red meat, fish, fruit, and vitamins C and E. Additional P values are as follows: ‡ indicates $P < 0.05$ for the comparison with the 0-to-15.9-km category; § indicates $P < 0.05$ for the comparisons with the 0-to-15.9-km and 16-to-31.9-km categories; ¶ indicates $P < 0.05$ for the comparisons with the 0-to-15.9-km, 16-to-31.9-km, and 32-to-47.9-km categories; * indicates $P < 0.05$ for the comparison with the 16-to-31.9-km category only; and † indicates $P < 0.05$ for the comparisons with the 0-to-15.9-km and 32-to-47.9-km categories. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert kilometers to miles, multiply by 0.6214.

increase of 0.134 ± 0.021 mg per deciliter (0.003 ± 0.0005 mmol per liter) in the HDL cholesterol concentration per kilometer run and decreases of 0.004 ± 0.001 in the ratio of total cholesterol to HDL cholesterol and of 0.04 ± 0.02 mm Hg in systolic blood pressure per kilometer run. Similar values were obtained when the initial circumferences of the waist, hip, and chest were used for adjustment.

DISCUSSION

The number of female runners that we studied was large and adds substantially to the total number in all previously published cross-sectional studies of running and lipoproteins in women.³² Because of the large sample, this study had the statistical power to test for in-

cremental increases in HDL cholesterol concentrations at levels of physical activity that exceed the current recommendations of the CDC. Mean plasma HDL cholesterol concentrations increased significantly with each 16-km increment in weekly running distance up to 48 km per week and at or above 64 km per week. Running at least 64 km per week was also associated with significantly lower body-mass-index values and waist and hip circumferences than running fewer kilometers. These data suggest that additional health benefits accrue to women who run longer distances (up to 64 km [40 miles] per week). The difference of 9.6 mg per deciliter (0.25 mmol per liter) in the mean HDL cholesterol concentration between the groups running the shortest distances (0 to 15.9 km per week) and the

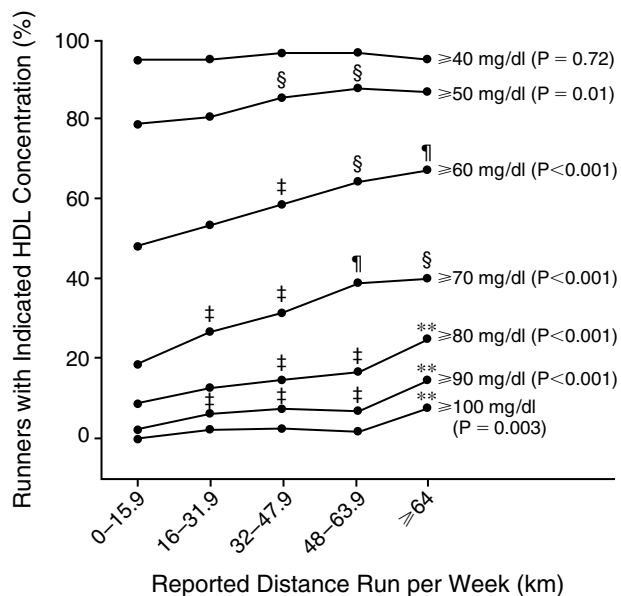


Figure 2. The Association between Distance Run and the Percentage of Women with Plasma HDL Cholesterol Values That Exceeded Specified Levels.

The P values shown in the figure are for a linear trend in the proportion of women having HDL cholesterol concentrations greater than or equal to the plotted value. See the legend to Figure 1 for an explanation of the symbols for additional P values; ** indicates $P < 0.05$ for the comparison with all distance categories below 64 km. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert kilometers to miles, multiply by 0.6214.

longest (≥ 64 km per week) may represent a 29 percent reduction in the risk of coronary heart disease and a 45 percent reduction in mortality from cardiovascular disease.³³

Our results appear to contradict the assertion in the CDC's guidelines that there is little additional benefit to increasing physical activity beyond the level attained by walking 2 miles (3.2 km) briskly most days of the week.¹ However, a meta-analysis of the studies cited in the CDC consensus statement has shown a linear decline in morbidity and mortality due to cardiovascular disease with increasing levels of leisure-time physical activity.³ These analyses provide no evidence that the benefits of increasing activity diminish at higher levels of activity. Extrapolating the results of the meta-analysis to long-distance runners is problematic, however, since few of the studies cited by the CDC involved very active men or women.

Both premenopausal and postmenopausal female runners would be expected to have higher concentrations of HDL cholesterol than their sedentary counterparts, since previous cross-sectional studies have reported significant effects of exercise in both groups of women.^{15-20,22,34} However, it is unclear from previous studies whether the magnitude of the effect of exercise is the same in the two groups.^{9,10} In our study, menstrual status did not affect the increases in HDL cholesterol induced by exercise. Postmenopausal estrogen replace-

ment also did not reduce the magnitude of the increase in the mean HDL cholesterol concentration with each additional kilometer run. It is unclear whether the concentrations of HDL cholesterol in women using oral contraceptives increased as their weekly running distances increased. Data from other studies suggest, however, that exercisers who use oral contraceptives may have smaller increases in HDL cholesterol than those who do not.²⁷

The National Runners' Health Study also included 8290 male runners, whose risk factors for coronary heart disease have been reported separately.⁶ The increase for women in HDL cholesterol per kilometer run is nearly identical to that reported for men (0.136 ± 0.006 mg per deciliter [0.004 ± 0.0002 mmol per liter] per kilometer per week). For each additional kilometer run, the decreases in systolic blood pressure, diastolic blood pressure, and body-mass index in men and women were also similar. As compared with men, women runners had significantly smaller decreases per kilometer run per week in the plasma concentrations of low-density lipoprotein cholesterol and triglycerides and in the ratio of total cholesterol to HDL cholesterol.

Our data contradict the idea that the generally higher HDL cholesterol concentrations in women (as compared with men) limit the potential for these levels to increase with exercise and that this ceiling effect accounts for the smaller increases in HDL cholesterol concentrations in women who exercise than in men.³⁵ In the current study, the increase in HDL cholesterol per kilometer run in women was almost identical to that in the men, despite their higher mean concentration of HDL cholesterol (63.6 ± 0.4 mg per deciliter [1.64 ± 0.01 mmol per liter], vs. 51.8 ± 0.2 mg per deciliter [1.34 ± 0.005 mmol per liter] in the men). Moreover, the data suggest that running increases HDL cholesterol throughout the upper range of the HDL cholesterol distribution. Women who ran 64 or more kilometers per week were significantly more likely to have HDL cholesterol concentrations above 100, 90, and 80 mg per deciliter than women who ran less. Moreover, the percentage of women with HDL cholesterol concentrations above these levels increased significantly as weekly running distance increased. The lack of a ceiling effect in the response of HDL cholesterol to exercise was also suggested in a previous clinical trial in men.³⁶

The cross-sectional associations of this report do not prove that running greater distances causes these reductions in risk factors. Well-designed randomized, controlled intervention studies have proved causality in men, but the data are less conclusive in women.³⁵ We controlled for the body-mass index when the women started running in order to eliminate the possibility that leaner women who had more favorable lipoprotein profiles may have chosen to run farther (i.e., a self-selection bias with respect to adiposity). When adjusted for base-line body-mass index, the associations of distance with the HDL cholesterol concentration, the ratio of total cholesterol to HDL cholesterol, blood pressure, and measures of adiposity all remained significant. It is pos-

sible that women with initially high levels of HDL cholesterol chose to run greater distances (self-selection due to high HDL cholesterol concentrations). Two separate studies have shown that base-line HDL cholesterol concentrations in sedentary men predict their weekly running distance during exercise training.^{36,37} Higher HDL cholesterol concentrations at base line may be a marker for men genetically endowed with types of muscle fiber that make running easier.³⁶⁻³⁸

The analyses reported here, in which we used measurements of risk factors for coronary heart disease that were supplied by the women's physicians, show detectable improvements in risk factors as commonly measured in medical practice. Thus, the associations between the distance run and risk factors for coronary heart disease are valid even when based on clinical measurements, which would be expected to be less precise than measurements made under research conditions. The added measurement error increases the likelihood of a false negative result, rather than a false positive one, and therefore yields conservative results.³⁹

Because less than 27 percent of women in this country meet the current CDC guidelines for physical activity,⁴⁰ increasing physical activity on the part of women is an important goal. It is unfortunate that the CDC recommendations have been widely interpreted to mean that there are few or no additional benefits to increasing vigorous exercise beyond the recommended levels. The findings of this study suggest that women obtain additional benefits at higher levels of exercise than currently recommended, benefits that accrue regardless of menstrual status or the use of postmenopausal estrogen replacement.

I am indebted to Davina Moussa, who provided much technical assistance, and to Amby Burfoot and Vern Walther of *Runner's World* magazine for their assistance in contacting many of the runners who participated in this study.

REFERENCES

- Pate RR, Pratt M, Blair SN, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 1995;273:402-7.
- American College of Sports Medicine. Guidelines for exercise testing and prescription. 4th ed. Philadelphia: Lea & Febiger, 1991.
- Williams PT. Physical activity and public health. *JAMA* 1995;274:533-4.
- Hahn RA, Teutsch SM, Rothenberg RB, Marks JS. Excess deaths from nine chronic diseases in the United States. *JAMA* 1990;264:2654-9.
- McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA* 1993;270:2207-12.
- Williams PT. Lipoproteins and adiposity show improvement at substantially higher exercise levels than those currently recommended. *Circulation* 1994; 90:1-471. abstract.
- Castelli WP. Cardiovascular disease in women. *Am J Obstet Gynecol* 1988; 158:1553-60.
- Williams PT, Krauss RM, Vranizan KM, Stefanick ML, Wood PD, Lindgren FT. Associations of lipoproteins and apolipoproteins with gradient gel electrophoresis estimates of high density lipoprotein subfractions in men and women. *Arterioscler Thromb* 1992;12:332-40.
- Brownell KD, Bachorik PS, Ayerle RS. Changes in plasma lipid and lipoprotein levels in men and women after a program of moderate exercise. *Circulation* 1982;65:477-84.
- Blumenthal JA, Matthews K, Fredrikson M, et al. Effects of exercise training on cardiovascular function and plasma lipid, lipoprotein, and apolipoprotein concentrations in premenopausal and postmenopausal women. *Arterioscler Thromb* 1991;11:912-7.
- LaRosa JC. Lipids and cardiovascular disease: do the findings and therapy apply equally to men and women? *Womens Health Issues* 1992;2: 102-13.
- Salonen JT, Puska P, Tuomilehto J. Physical activity and risk of myocardial infarction, cerebral stroke and death: a longitudinal study in Eastern Finland. *Am J Epidemiol* 1982;115:526-37.
- Lapidus L, Bengtsson C. Socioeconomic factors and physical activity in relation to cardiovascular disease and death: a 12 year follow up of participants in a population study of women in Gothenburg, Sweden. *Br Heart J* 1986;55:295-301.
- Wood PD, Haskell WL, Stern MP, Lewis S, Perry C. Plasma lipoprotein distributions in male and female runners. *Ann NY Acad Sci* 1977;301:748-63.
- Moore CE, Hartung GH, Mitchell RE, Kappus CM, Hinderlitter J. The relationship of exercise and diet on high-density lipoprotein cholesterol levels in women. *Metabolism* 1983;32:189-96.
- Stamford BA, Matter S, Fell RD, Sady S, Cresanta M, Papanek P. Cigarette smoking, physical activity, and alcohol consumption: relationship to blood lipids and lipoproteins in premenopausal females. *Metabolism* 1984;33:585-90.
- Upton SJ, Hagan RD, Lease B, Rosentsweig J, Gettman LR, Duncan JJ. Comparative physiological profiles among young and middle-aged female distance runners. *Med Sci Sports Exerc* 1984;16:67-71.
- Hartung GH, Reeves RS, Foreyt JP, Patsch W, Gotto AM Jr. Effect of alcohol intake and exercise on plasma high-density lipoprotein cholesterol subfractions and apolipoprotein A-I in women. *Am J Cardiol* 1986;58:148-51.
- Morgan DW, Cruise RJ, Girardin BW, Lutz-Schneider V, Morgan DH, Qi WM. HDL-C concentrations in weight-trained, endurance-trained, and sedentary females. *Physician Sportsmed* 1986;14:166-81.
- Kaiserauer S, Snyder AC, Sleeper M, Zierath J. Nutritional, physiological, and menstrual status of distance runners. *Med Sci Sports Exerc* 1989;21: 120-5.
- Owens JF, Matthews KA, Wing RR, Kuller LH. Physical activity and cardiovascular risk: a cross-sectional study of middle-aged premenopausal women. *Prev Med* 1990;19:147-57.
- Hartung GH, Moore CE, Mitchell R, Kappus CM. Relationship of menopausal status and exercise level to HDL cholesterol in women. *Exp Aging Res* 1984;10:13-8.
- Podl TR, Zmuda JM, Yurgalevitch SM, et al. Lipoprotein lipase activity and plasma triglyceride clearance are elevated in endurance-trained women. *Metabolism* 1994;43:808-13.
- Bush TL, Barrett-Connor E, Cowan LD, et al. Cardiovascular mortality and noncontraceptive use of estrogen in women: results from the Lipid Research Clinics Program Follow-up Study. *Circulation* 1987;75:1102-9.
- Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J* 1986;11:383-90.
- Brunner D, Weisbort J, Meshulam N, et al. Relation of serum total cholesterol and high-density lipoprotein cholesterol percentage to the incidence of definite coronary events: twenty-year follow up of the Donolo-Tel Aviv Prospective Coronary Artery Disease Study. *Am J Cardiol* 1987;59:1271-6.
- Suter E, Marti B. Little effect of long-term, self-monitored exercise on serum levels in middle-aged women. *J Sports Med Phys Fitness* 1992;32:400-11.
- Lindheim SR, Notelovitz M, Feldman EB, Larsen S, Khan FY, Lobo RA. The independent effects of exercise and estrogen on lipids and lipoproteins in postmenopausal women. *Obstet Gynecol* 1994;83:167-72.
- Haskell WL, Camargo C Jr, Williams PT, et al. The effect of cessation and resumption of moderate alcohol intake on serum high-density lipoprotein subfractions: a controlled study. *N Engl J Med* 1984;310:805-10.
- Seidell JC, Cigolini M, Charzewska J, Ellsinger BM, di Biase G. Fat distribution in European women: a comparison of anthropometric measurements in relation to cardiovascular risk factors. *Int J Epidemiol* 1990;19:303-8.
- Miller RG Jr. Beyond ANOVA, basics of applied statistics. New York: John Wiley, 1986.
- Krummel D, Etherton TD, Peterson S, Kris-Etherton PM. Effects of exercise on plasma lipids and lipoproteins of women. *Proc Soc Exp Biol Med* 1993;204:123-37.
- Gordon DJ, Probstfield JL, Garrison RJ, et al. High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies. *Circulation* 1989;79:8-15.
- Rainville S, Vaccaro P. The effects of menopause and training on serum lipids. *Int J Sports Med* 1984;5:137-41.
- Lokey EA, Tran ZV. Effects of exercise training on serum lipid and lipoprotein concentrations in women: a meta-analysis. *Int J Sports Med* 1989;10:424-9.
- Williams PT, Stefanick ML, Vranizan KM, Wood PD. The effects of weight loss by exercise or by dieting on plasma high-density lipoprotein (HDL) levels in men with low, intermediate, and normal-to-high HDL at baseline. *Metabolism* 1994;43:917-24.
- Williams PT, Wood PD, Haskell WL, Vranizan K. The effects of running mileage and duration on plasma lipoprotein levels. *JAMA* 1982;247:2674-9.
- Williams PT. High density lipoproteins and lipase activity in runners. *Atherosclerosis* 1993;98:251-4.
- Fuller WA. Measurement error models. New York: John Wiley, 1987:4.
- Prevalence of recommended levels of physical activity among women — Behavioral Risk Factor Surveillance System, 1992. *MMWR Morb Mortal Wkly Rep* 1995;44:105-7, 113.