The Relationships of Vigorous Exercise, Alcohol, and Adiposity to Low and High High-Density Lipoprotein-Cholesterol Levels

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While vigorous exercise, alcohol, and weight loss are all known to increase high-density lipoprotein-cholesterol (HDL-C), it is not known whether these interventions increase low HDL as effectively as has been demonstrated for normal HDL. This report tests the hypothesis that there may be differences in the calculated response of men and women with low versus high HDL-C to exercise, alcohol, and weight loss across the spectrum of HDL-C levels. Physican-supplied medical data from 7,288 men and 2,326 women were divided into deciles of self-reported vigorous exercise, alcohol intake, body mass index (BMI), or body circumferences. Within each decile we determined the percentiles of the HDL distributions and average running distance, alcohol intake, BMI, or body circumference. Simple least-squares regression analysis was then used to estimate the slope for kth HDL percentile (k = 5%, 6%, . . .,95%) versus running distance, alcohol intake, BMI, or body circumference across deciles. Bootstrap resampling was used to estimate standard errors and statistical significance for the regression lines. In both sexes, the increase in HDL-C per unit alcohol intake was at least twice as great at the 95th as at the 5th percentile of the HDL distribution. There was also a significant graded increase from the 5th to the 95th HDL percentile for the slopes relating HDL to exercise (km run) and alcohol intake. Men's HDL-C declined in association with fatness (BMI, waist, and chest circumference) more sharply at the 95th than at the 5th percentile of the HDL distribution. The results of this study suggest that the effects of physical activity, alcohol, and weight reduction on HDL-C levels may be, to a large extent, dependent on the initial level with the greatest improvement achieved in subjects with high HDL and the least improvement in those having low HDL-C levels.

HYGIENIC APPROACHES to increasing high-density lipoprotein-cholesterol (HDL-C) include physical activity, weight loss, and smoking cessation.[1] Alcohol also increases HDL-C, but promoting moderate alcohol intake must be weighed against the risks of excess consumption.[2]

Much of what is known about the relationships of HDL-C to exercise, weight loss, and alcohol intake is based on group (average) responses to experimental manipulations (intervention studies) or relationships between average HDL and these variables in a population (cross-sectional studies). Regression curves are often used to describe the dose-response relationships between HDL-C and alcohol, physical activity, and adiposity. The curves represent the expected HDL level at a given level of consumption, caloric expenditure, or fatness. Differences between the actual observations and the regression curve are presumed to represent random variation or error. If the differences do not represent random variation, then the single regression curve may ignore important aspects of the relationships that are germane to their physiologic understanding and public health significance. For example, the HDL response at the more extreme values may be more important than the average response because they represent individuals at greatest or least health risk.[3]

In this report, we test the hypothesis that there may be differences in the estimated response of men and women with low versus high HDL-C to exercise, alcohol, and weight loss across the spectrum of HDL-C levels. Individual variation in HDL-C response to interventions may be dependent upon genetic factors affecting both baseline HDL-C and efficacy of the interventions.[4-9]

MATERIALS AND METHODS

The design and subject characteristics of this cohort are described in detail elsewhere.[10,11] Briefly, all participants completed a 2-page questionnaire, distributed nationally at races and to subscribers of the nation's largest running magazine (Runners' World, Emmaus, PA). This questionnaire solicited information on demographics, running history, weight history, diet, cigarette use, medical history, and medications. HDL-C levels were obtained from the medical records of 7,288 male and 2,326 female nonvegetarian, nonsmoking runners without prior history of heart disease or cancer, who did not report using any medications that might affect HDL-C levels.

Average number of kilometers run per day was calculated by averaging the reported distances for the preceding 5 years. The test-retest correlations for self-reported distance run ($r = 0.89$, unpublished data from 110 runners who completed duplicate questionnaires several months apart) compares favorably with those reported for the Minnesota Leisure Time Physical Activity Questionnaire[12] and other physical activity questionnaires.[13,14] Body mass index (BMI) was calculated as the weight in kilograms divided by height in meters squared. Two approaches were used to validate questions on anthropometric measurements from 110 men: (1) test-retest correlations from duplicate questionnaires and (2) correlations of clinical measurements of height, weight, and circumference measurements with their self-reported values. Self-reported height and weight showed strong agreement with the duplicate questionnaires ($r = 0.98$ and $r = 0.97$, respectively) and with their clinic measurements ($r = 0.96$ for both). There were reasonable, but somewhat weaker, correlations for self-reported body circumferences with their second self-reported measurement (waist: $r = 0.84$; hip: $r = 0.79$; chest: $r = 0.93$) and with their clinic measurements

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(waist: $r = 0.68$; hip: $r = 0.63$; chest: $r = 0.77$). The somewhat weaker reproducibility of the circumference measurements means that the probability of a statistical type II error (false negative) will be greater than for height and weight, but this should not affect the probability of the type I statistical error (false positive).[15]

Amount of alcohol consumed per week was calculated on the basis of 14.2 mL per 12 oz bottle of beer or 4-oz glass of wine, and 17.7 mL per drink of hard liquor.[16] Self-reported alcohol consumption was validated by correlating reported usual weekly intakes from the questionnaires with recorded actual intakes from 4-day food records ($r = 0.65$ in 110 men).

Statistical Analyses

The statistical approach, originally developed to study the relationship of adiposity to running distance[17] and triglycerides to adiposity,[18] was modified to study the increase in HDL per kilometer run as follows: we divided the data into 10 deciles of running distance (i = 1 . . .10), and within each decile we determined the kth percentile of the HDL-distribution ($HDL_{[k]i}$) and average running distance ($\overline{\text{running distance}}_i$), where the kth percentiles included all integer values between the 5th and 95th percentile inclusively. Combining these values across deciles yielded 10 bivariate observations ($HDL_{[k]i}$, $\text{running distance}_i$; i = 1 . . .10) for each percentile "k" of the HDL distribution (Figs 1 and 2). Simple least-squares regression analysis was then used to estimate the slope for kth HDL percentile (dependent variable_i) versus running distance (independent variable) from the 10 bivariate observations. This slope represents the increase in HDL per kilometer increment in running distance. The same approach was employed to determine the relationships of HDL-C to alcohol intake, BMI, and body circumferences.

Because the usual underlying statistical assumptions presumably do not apply for percentiles (particularly those representing the tails of the distribution), we calculated the standard errors and significance levels by bootstrap resampling.[19] Bootstrap estimates were created as follows: (1) within each decile, we sampled with replacement to create a bootstrap data set of the independent variable and HDL-C, from which we determined the kth HDL percentile and the average for the independent variable; (2) across the 10 deciles, least squares regression was applied to estimate the apparent change in HDL per unit increment in the independent variable at the kth HDL percentile, k = 5th, 6th, . . . 95th; (3) steps 1 and 2 were repeated 10,000 times. The standard errors for the regression slopes were calculated as the standard deviation of the slopes from the 10,000 bootstrap samples.[19]

If running greater distances (drinking more or being leaner) is associated with the same HDL change regardless whether the individual's HDL is relatively high or low, then the regression slopes at the kth percentile of HDL will be the same for all k (ie, parallel). Different (ie, nonparallel) regression slopes could indicate that these variables affect various portions of the HDL distribution differently. Bootstrap resampling was used to test whether the slopes increased or decreased progressively from the 5th to the 95th percentiles of the HDL distribution. This was done by constructing a numerical contrast among the slopes that increased linearly with the percentile (ie, −45, −44, . . ., 44, 45) for each bootstrap sample. Two-tailed significance levels were calculated as 2*minimum (P, 1-P), in which P is the proportion of times that the bootstrap slopes or linear contrasts were less than zero. In the results and discussion to follow, "slope" refers exclusively to the change in HDL at the kth percentile per unit increment in the independent variable, and "trend" refers exclusively to whether these slopes increase or decrease progressively from the 5th through the 95th percentile of the HDL-C distribution.

Figure 3 includes a plot of the male slopes adjusted to the percentile distribution of the females using a Q-Q plot of the male/female HDL distribution.[20] For example, the 50th percentile of the men's HDL distribution (1.293 mmol/L) corresponds to the 18.5th percentile of the female distribution. Therefore, we replotted the men's slope for HDL versus BMI at the 50th percentile of the HDL distribution (−0.030 mmol/L per kg/m^2) at the 18.5th percentile to assess whether the women's higher HDL-C explained the differences between sexes. This adjustment of the men's HDL-C distribution was repeated for all points, yielding the dashed curve for the men on each of the figures (the HDL-C at the men's 95th percentile corresponds to the women's 81st percentile, thus the adjusted men's curves extends only as far as the 81st percentile).

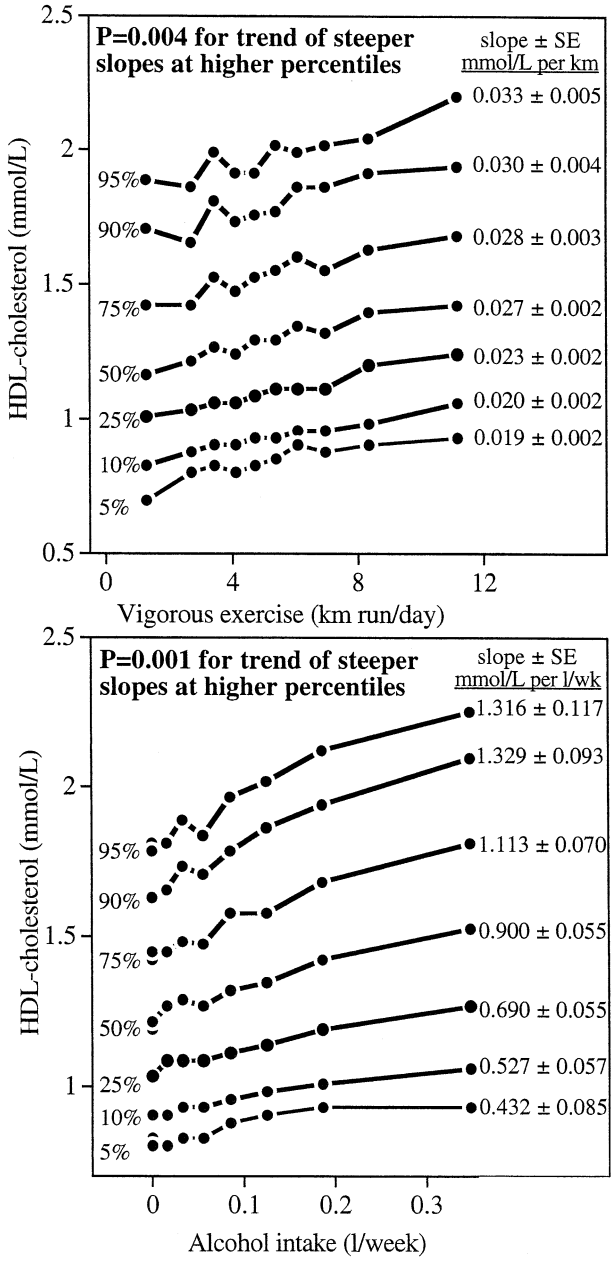

Fig 1. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of plasma HDL-C concentrations by deciles of reported kilometer run per day (N = 7,066) and alcohol intake (N = 7,065) in male runners. The regression slopes ± SE (listed on the right) were all significant at $P < .001$.

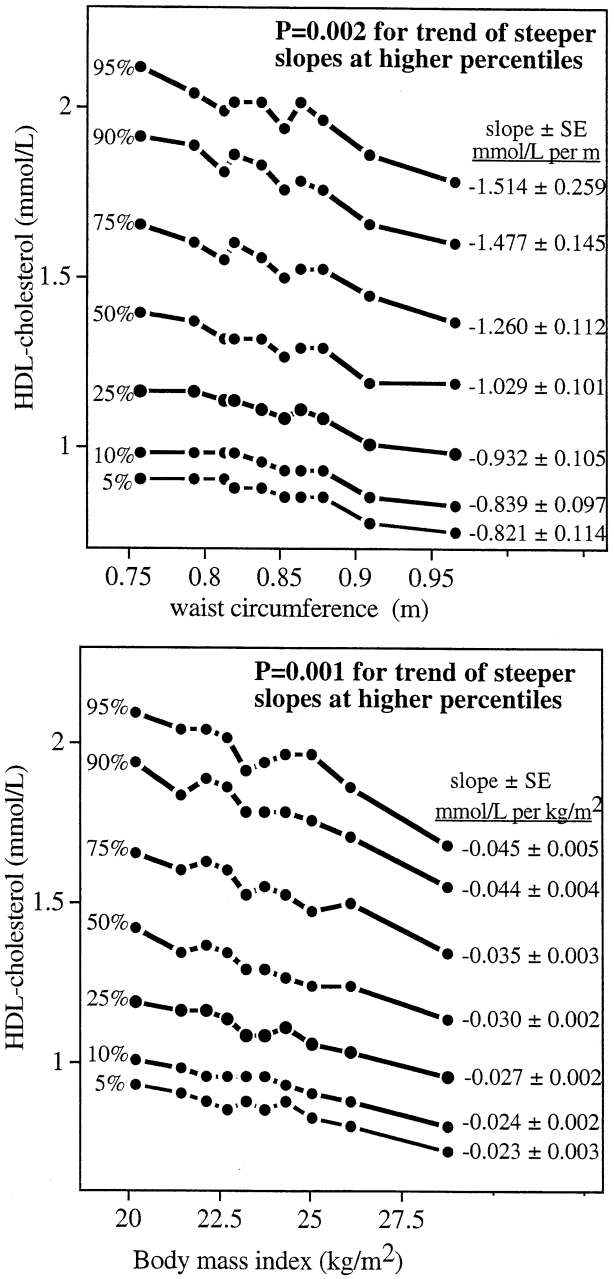

Fig 2. The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of plasma HDL-C concentrations by deciles of body mass index (N = 6,926) and waist circumference (N = 6,770) and in male runners. The regression slopes ± SE (listed on the right) were all significant at *P* < .001.

It was necessary to verify that the statistics and software did not produce significant results due to statistical or programming artifacts. This was done by simulating data where the relationships of HDL to vigorous exercise, BMI, waist circumference, and alcohol were given by their linear regression slope only. Specifically: (1) the simple linear relationship between HDL and the independent variable was estimated by standard least squares regression for the original data set; (2) a data set of residuals was created; (3) each observed HDL-C was replaced with the sum of 2 terms: its expected level (calculated from the linear regression equation and the value of the independent variable) and a randomly assigned residual term. Ten thousand replicates of the simulated data were created and tested. These simulated HDL should exhibit parallel regression lines at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles. Indeed, the regression slopes were significantly different from zero, but there were no differences in the regression slopes at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles (parallel, as required).

RESULTS

The sample consisted of men and women who exercised vigorously (mean±SD, 38.0 ± 20.2 and 34.7 ± 19.9 km run per week, respectively). Correspondingly they tended to have desirable BMI (men: 23.78 ± 2.48 kg/m^2; women: 21.33 ± 2.48 kg/m^2), waist (men: 0.849 ± 0.060 m; women: 0.686 ± 0.069 m), hip (men: 0.952 ± 0.071 m; women: 0.919 ± 0.065 m), and chest circumferences (men: 1.016 ± 0.069 m; women: 0.880 ± 0.053 m). Twenty-six percent of the men and 6% of the women were at least moderately overweight (BMI ≥ 25 kg/m^2). The men consumed an average (± SD) of 85.54 ± 115.25 mL alcohol per week and the women consumed about a third less (53.78 ± 79.66 mL/wk). Mean plasma HDL concentrations were 1.34 ± 0.35 mmol/L (51.7 ± 13.5 mg/dL) in men and 1.65 ± 0.41 mmol/L (63.7 ± 15.8 mg/dL) in women.

Figures 1 and 2 display the relationships of the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the men's HDL-C distribution to the amount of vigorous exercise, alcohol intake, BMI, and waist circumference. Specifically, the data were divided into deciles of the independent variable (alcohol, running distance, adiposity), and within each decile we plotted the point representing the kth HDL-C percentile (Y-axis) versus the average of the independent variable (X-axis). Line segments were used to connect the kth percentile from the first to the tenth decile. The slopes and their standard errors from 10,000 bootstrap samples are presented at the right. Table 1 presents the slopes (± SE) for both men and women for these variables and 2 additional body circumference measurements (hip and chest circumferences). Significance levels are indicated for each slope and for the test of whether a significant linear trend exists for the magnitude of the slope (increasing or decreasing) from the 5th through the 95th percentile of the HDL distribution. Specifically, these significance levels test whether the regression slopes at the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile are parallel (null hypothesis) or increased or decreased progressively when traversing from the 95th to the fifth percentile.

Figure 3 plots the individual slopes for the change in HDL-C associated with a 1-unit increment in the alcohol, running distance, BMI, and body circumferences (Y-axis) for the 5th through the 95th percentiles of the men's and women's HDL-C distribution (X-axis). For example, Table 1 shows that the increase in women's HDL-C per km/d run was 0.006 mmol/L (0.24 mg/dL) at the 5th percentile and 0.027 mmol/L (1.05 mg/dL) at the 95th percentile of the HDL distribution. These values are plotted in the upper left panel of Fig 3 along with the slopes at all intervening percentiles.

Figure 4 tests whether the slopes at any 2 percentiles of the HDL distribution are significantly different from each other. Each point on the plot represents a comparison between the

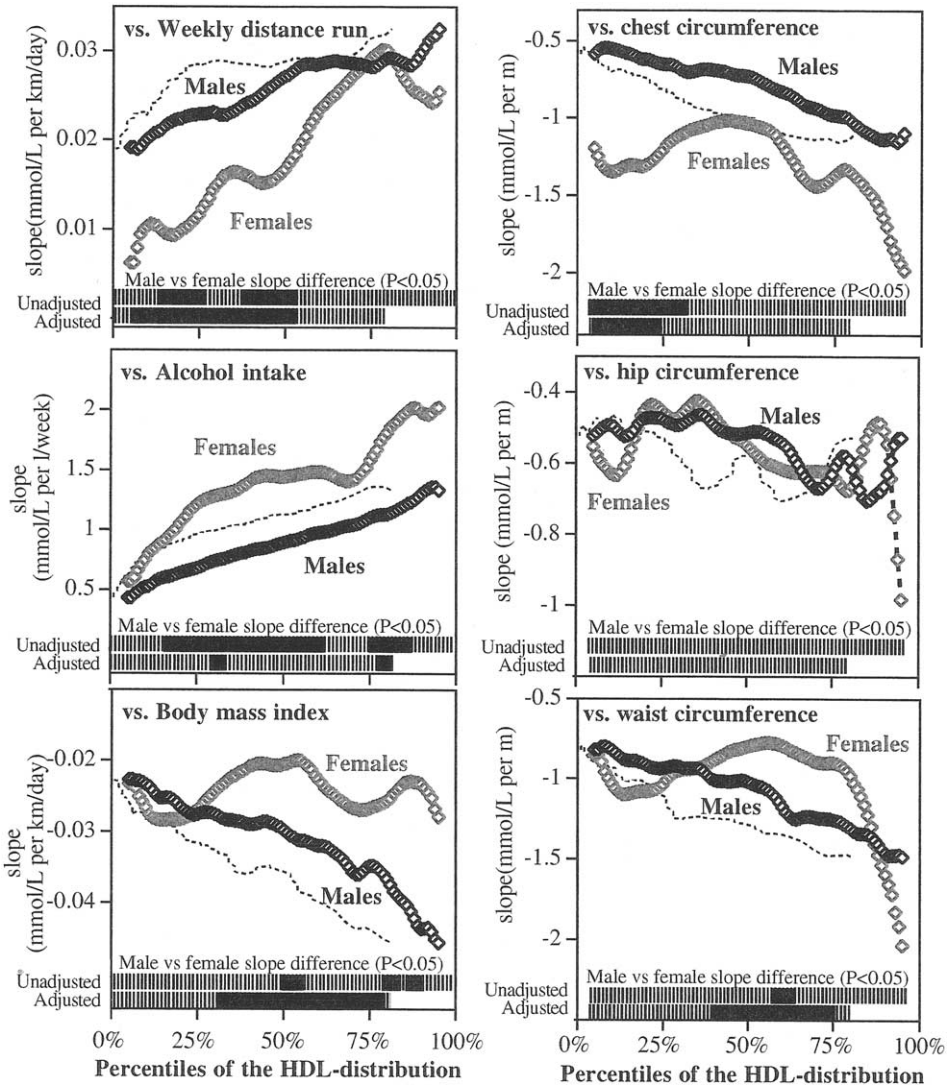

Fig 3. Plot of the regression slopes for male and female HDL-C (mmol/L) *v* alcohol intake, running distance, BMI (kg/m^2), and circumferences of the waist, hip, and chest at all percentile of the HDL-C distribution. Dashed line designates the men's slopes adjusted to the women's cumulative HDL-C distribution. Bars at the bottom of each graph designate significant differences between men and women's slopes when matched by HDL percentile (unadjusted) and HDL-C concentration (adjusted).

slopes at 2 different percentiles of the HDL distribution, one represented by the X-coordinate and one represented by the Y-coordinate. White areas represents the percentile combinations (X,Y) having slopes that were not significantly different from each other, shaded regions designate percentile combinations that have slopes that differ significantly from each other at $P \leq .05$, and solid black regions designate percentile combinations that have slopes that differ significantly at $P \leq .01$. For example, the increase in HDL-C per km/d run at the 50th HDL percentile (0.027 ± 0.002 mmol/L or 1.06 ± 0.08 mg/dL) was significantly greater than the increase at the 25th HDL percentile (0.023 ± 0.002 mmol/L or 0.88 ± 0.07 mg/dL, $P \leq .05$), represented by shaded region) and at the 5th percentile (0.019 ± 0.003 mmol/L or 0.73 ± 0.10 mg/d, $P \leq .01$ represented by a solid black region).

Vigorous Exercise

Table 1 shows that the average increase (± SE) in the median HDL-C (50th percentile) per km/d run was 0.027 ± 0.002 mmol/L (1.06 ± 0.08 mg/dL) in men and 0.018 ± 0.004 mmol/L (0.67 ± 0.15 mg/dL) in women. The men's slopes were steepest at the 95th percentile and become progressively weaker going from the 95th to the 5th percentile (Fig 1). The calculated increase in HDL-C per km run was over 70% larger at the 95th percentile than at the 5th percentile of the HDL-distribution in men (0.033 ± 0.005 *v* 0.019 ± 0.002 mmo1/L or 1.27 ± 0.19 *v* 0.74 ± 0.10 mg/dL), and over 4-fold greater at the 95th than at the 5th percentile in women (Table 1). In both sexes, the test statistic for nonparallel regression slopes was significant ($P = .004$ in men; $P = .005$ in women) suggesting that the calculated increase in HDL-C per km/d run was dependent upon whether HDL levels were low or high relative to others in the population.

Figure 3 presents a detailed plot of the regression slopes for the increase in HDL-C versus km/d (Y-axis) at the 5th, 6th, . . . 95th percentiles of the HDL distribution (X-axis). The individual slopes were significantly different from zero for all percentiles between the 5th and 95th percentile in men ($P < .0001$)

Table 1. Regression Slopes (± SE) for HDL-C (mmol/L) Versus Weekly Running Distance, Alcohol Intake, BMI, and Waist Circumference in Vigorously Active Men and Women for Different Percentiles of the HDL Distribution

	Regression Slope at Different Percentile of the Distribution							Trend in Slopes (*P*)
	5%	10%	25%	50%	75%	90%	95%	
Daily running distance (mmol/L per km/d)								
Men	0.019 ± 0.002‡	0.020 ± 0.002‡	0.023 ± 0.002‡	0.027 ± 0.002‡	0.028 ± 0.003‡	0.030 ± 0.004‡	0.033 ± 0.005‡	.004
Women	0.006 ± 0.008	0.010 ± 0.005*	0.012 ± 0.005†	0.018 ± 0.004‡	0.030 ± 0.006‡	0.025 ± 0.009†	0.027 ± 0.010†	.005
Alcohol intake (mmol/L per L/wk)								
Men	0.432 ± 0.085‡	0.527 ± 0.057‡	0.690 ± 0.055‡	0.900 ± 0.055‡	1.113 ± 0.070‡	1.329 ± 0.093‡	1.316 ± 0.117‡	.001
Women	0.570 ± 0.174‡	0.801 ± 0.133‡	1.234 ± 0.146‡	1.445 ± 0.194‡	1.626 ± 0.253‡	1.966 ± 0.321‡	2.013 ± 0.377‡	.001
BMI (mmol/L per kg/m^2)								
Men	−0.023 ± 0.003‡	−0.024 ± 0.002‡	−0.027 ± 0.002‡	−0.030 ± 0.002‡	−0.035 ± 0.003‡	−0.044 ± 0.004‡	−0.045 ± 0.005‡	.001
Women	−0.023 ± 0.006‡	−0.028 ± 0.004‡	−0.027 ± 0.005‡	−0.020 ± 0.005‡	−0.027 ± 0.006‡	−0.024 ± 0.008‡	−0.029 ± 0.014*	.89
Waist circumference (mmol/L per m)								
Men	−0.821 ± 0.114‡	−0.839 ± 0.097‡	−0.932 ± 0.105‡	−1.029 ± 0.101‡	−1.260 ± 0.112‡	−1.477 ± 0.145‡	−1.514 ± 0.259‡	.002
Women	−0.853 ± 0.216‡	−1.065 ± 0.173‡	−1.008 ± 0.214‡	−0.792 ± 0.155‡	−0.905 ± 0.203‡	−1.654 ± 0.266‡	−2.231 ± 0.484‡	.17
Hip circumference (mmol/L per m)								
Men	−0.524 ± 0.109‡	−0.493 ± 0.110‡	−0.475 ± 0.100‡	−0.515 ± 0.111‡	−0.631 ± 0.162‡	−0.664 ± 0.214†	−0.528 ± 0.246*	.34
Women	−0.553 ± 0.246*	−0.628 ± 0.208†	−0.451 ± 0.178†	−0.548 ± 0.192‡	−0.633 ± 0.206†	−0.508 ± 0.313	−0.983 ± 0.558	.37
Chest circumference (mmol/L per m)								
Men	−0.593 ± 0.096‡	−0.566 ± 0.074‡	−0.643 ± 0.072‡	−0.744 ± 0.083‡	−0.997 ± 0.104‡	−1.142 ± 0.139‡	−1.141 ± 0.262‡	.001
Women	−1.195 ± 0.261‡	−1.347 ± 0.285‡	−1.207 ± 0.227‡	−1.038 ± 0.216‡	−1.368 ± 0.290‡	−1.700 ± 0.438‡	−1.984 ± 0.546‡	.30

NOTE. Presented values are the regression coefficient and SE from 10,000 bootstrap samples.

*$P \leq .05$.

†$P \leq .01$.

‡$P \leq .001$.

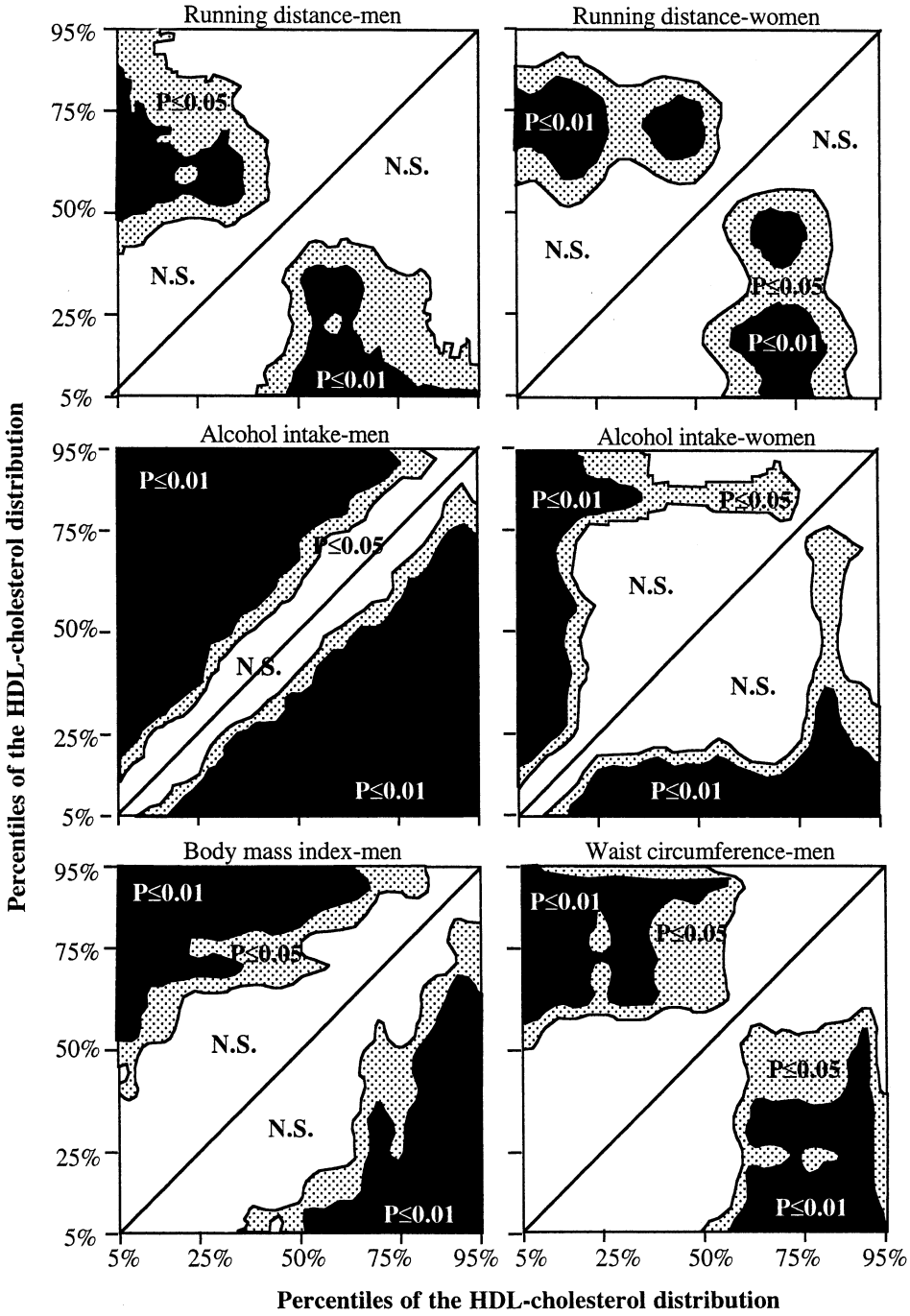

Fig 4. Plots of the statistical significances of the differences in slope at the jth and kth percentiles of the HDL distribution (j,k = 5th, 6th, . . .95th percentile) for HDL-C (dependent variable) *v* running distance, alcohol intake, and adiposity. White areas represent pairs of percentiles having slopes that were not significantly different from each other. Shaded areas represent pairs of percentiles having slopes that differ significantly from each other at $P \leq .05$. Solid black areas represent pairs of percentiles having slopes that differ significantly from each other at $P \leq .01$. The graphs are necessarily symmetric across the diagonal.

and between the 9th and 95th percentiles in women ($P < .05$). Both the men's and women's curves show a definite trend towards steeper slopes as the percentile of the HDL distribution increased from the 5 through the 95th percentiles (trend strongest from the 5th to the 50th percentile in men and from the 5th to the 85th percentile in women). Figure 4 presents the significance of the pairwise comparisons between slopes at all percentiles between 5% and 95%. The nonwhite (shaded and solid) regions of the graph show that the slopes were generally significantly lower for HDL-C below the 35th percentile vis-a-vis HDL between the 45th and 80th percentile in men, and significantly lower for HDL-C below the 50th percentile vis-a-vis HDL between the 55th and 90th percentile in women.

Alcohol Intake

In both men and women, greater weekly intakes of alcohol were associated with significantly higher HDL-C at all percentiles ($P \leq .001$, Table 1). The regression slopes became progressively larger as the percentile of the HDL distribution

increased from lowest to highest in men ($P = .001$, see Fig 1) and women ($P = .001$, Table 1). The increase in HDL per L/week consumed was over 3-fold greater at the 95th percentile than at the 5th percentile in both men and women (Table 1). Figure 3 shows that the trend for progressively higher slopes from the lowest to the highest HDL percentile was essentially linear in men, but somewhat less linear in women. The pairwise comparisons of Fig 4 show that in men the increase in HDL-C per liter of alcohol consumed differed significantly whenever there was a 15% to 20% difference in the HDL-C percentiles. In women, the rate that HDL-C increased per unit of alcohol consumed was significantly greater above the 25th percentile of the women's HDL-C distribution vis-a-vis below the 15th percentile, and above the 80th percentile vis-a-vis lower percentiles.

BMI and Body Circumference

At each population percentile, HDL-C declined significantly in association with larger BMI and larger waist and chest circumferences regardless of sex (Table 1). In men, the decline in HDL-C was significantly greater at the higher percentiles of the HDL-distribution than at the lower percentiles when plotted against BMI and chest and waist circumferences (nearly twice as great at the 95th than at the 5th percentile). The slopes relating HDL-C to BMI, waist circumference, and chest circumference became progressively more negative from the 5th through the 95th percentile (Fig 3). Unlike men, the declines in women's HDL-C with incremental increases in BMI were similar at both the lower and higher portions of their HDL-C distribution (ie, the regression slopes did not progressively change as the percentile of the HDL distribution went from the 5th to the 95th percentile). Figure 4 displays whether the difference in slopes for HDL-C versus BMI is significant for all pairwise comparisons between percentiles. The plot suggests that at higher percentiles of the HDL distribution, a smaller difference in percentiles is required to achieve a significant difference in slopes than at the lower percentiles of the HDL distribution. Figure 4 also presents the regions of significant difference in slopes for men's HDL-C versus waist circumferences. The region of significance is rectangular in shape, suggesting that the slopes for percentiles above the 55th percentile are significantly more negative than the slopes at or below the median of the HDL distribution.

Male-Female Differences

Figure 3 compares the men's and women's slopes for HDL-C versus running distance, alcohol, and adiposity at each percentile of the HDL distribution (ie, $\text{slope}_{\text{men's kth percentile}}$ *v* $\text{slope}_{\text{women's kth percentile}}$, k = 5th. . . 95th percentile). Significant differences ($P < .05$) between the men's and women's slopes are designated by the solid portions of the bar at the bottom of each graph, marked unadjusted). When matched by sex-specific population percentiles, it would appear that for portions of the HDL-distribution, the relationship is more pronounced in men than women for running distance and chest circumference and more pronounced in women than men for alcohol intake.

To test whether these differences between the male and female slopes are due to the fact that at any given percentile, women have a higher HDL-C value than men, we replotted the male's curves to correspond to the female cumulative percentiles (dashed lines of Fig 3, see Materials and Methods). Comparing the adjusted male curve to the female curve tests whether the slopes for men and women are the same or different when matched by HDL-C concentrations. The solid portions of the bar marked "adjusted" at the bottom of the graph designate significant differences ($P < .05$) between the adjusted men's slopes and the women's slope. The adjustment eliminated about half of the difference between the male and female slopes for alcohol, while further accentuating the male-female difference in slopes for distance run, BMI, and waist circumference.

DISCUSSION

The analyses suggest that the relationships of HDL-C to alcohol, exercise, and weight are more complex than previously described. They suggest that increases in HDL-C associated with alcohol intake and vigorous exercise and declines in HDL-C associated with adiposity were disproportionately due to large increases (or decreases) affecting the higher percentiles of the HDL distribution. The results suggest that interventions that use physical activity, alcohol, or weight reduction to increase HDL-C may find that the effects are dependent upon initial levels, with the greatest improvement achieved in those already having high HDL and the least improvement in those most at risk due to low HDL-C. To our knowledge, these are the first analyses to show that the cross-sectional associations of HDL versus exercise, adiposity, or alcohol do not apply uniformly throughout the HDL distribution. The analyses suggest that men and women with higher HDL-C levels are likely to be the most responsive to nonpharmacologic interventions to increase HDL. This is in contrast to statin therapies, which are reported to produce increases in HDL-C that are relatively constant through the range of baseline values.[21]

The etiology of low HDL is only partially understood. Polygenic inheritance is estimated to account for between 35% to 50% HDL-C variability (57% for hypolipoproteinemia), although to date few specific genes associated with low HDL have been identified.[22,23] Much of the variation in HDL has been attributed to environmental factors or to triglyceride levels. Low plasma concentrations of HDL-C are usually associated with elevated plasma triglyceride-rich lipoproteins,[24] which promote the exchange of HDL-cholesteryl ester for triglycerides via cholesteryl ester transfer protein.[25] Lipolysis of the HDL-triglycerides by hepatic lipase leads to the formation of smaller HDL particles. These smaller particles are catabolized and cleared more rapidly than larger particles.[26,27]

Despite convincing evidence that physical activity increases average HDL-C,[28,29] its efficacy for correcting low HDL is suspect. In an earlier post hoc analysis of initially sedentary men assigned to conditions of either exercise (primarily running) or control for 1 year, men with relatively low HDL-C ($\leq$37 mg/dL or $\leq$0.96 mmol/L) had a nonsignificant mean increase in their HDL-C (2.3 $\pm$ 1.9 mg/dL or 0.06 $\pm$ 0.05 mmol/L), whereas those who had relatively higher HDL-C ($\geq$48 mg/dL or $\geq$1.24 mmol/L) had increases that were 3-fold greater (7.0 $\pm$ 1.3 mg/dL or 0.18 $\pm$ 0.03 mmol/L).[30] The current cross-sectional analyses suggest that the increase in HDL at the fifth percentile was only 0.73 mg/dL (0.019 mmol/L) per kilometer increment in daily distance run. However, the increase in men with

high HDL was twice as great. This does not imply that low HDL men should refrain from physical activity, given the overwhelming evidence that physically active men are at less risk of heart disease than sedentary men.[31] Moreover, it has been reported that the percentage of men with HDL-C < 35 mg/dL (<0.91 mmol/L) is reduced by 5-fold for those averaging 80 km/wk of running or more as compared with under 16 km/wk[10] (however, this difference probably includes effects due to self selection, discussed below). Although relationships between genes and HDL training responses have been reported, these include greater HDL-C increases in genes associated with low HDL-C (endothelial lipase[9]), genes unrelated to baseline HDL-C (cholesteryl-ester transfer protein[7]), and genes associated with slightly higher HDL-C (apolipoprotein [apo]E2[8]). Thus, our existing knowledge of the relationship of genes to baseline HDL levels and training effects is inadequate to explain the relationships reported here.

The analyses presented in this report support an earlier observation that sedentary men with initially low HDL have at best modest increases in HDL when they exercise vigorously.[30] In addition, the analyses address 2 previously unresolved issues. First, Williams et al[30,32] initially speculated that men with low baseline HDL may have achieved smaller increases in HDL-C during 1 year of training because they ran less. This speculation is consistent with 2 separate intervention trials that have shown that low baseline HDL-C predicts low weekly running distances during subsequent training.[30,32] Lower HDL-C levels at baseline may be a marker for men who find running more difficult because of intrinsic factors affecting their performance, such as lower proportions of slow twitch red muscle fibers.[33] The analyses presented in the current report are based on reported distances run. Thus, low HDL-C levels appear to show less of a response to running even in individuals who report running significant distances. Second, the analyses presented in the current report show that the resistance to increasing HDL is not simply limited to the modest exercise levels achieved in the earlier intervention study,[30] but appears to apply throughout the range of running distances.

Zmuda et al[34] also reported that when compared with men with normal HDL-C, those with low baseline HDL had smaller increases in HDL-C and HDL_2, smaller increases postheparin lipoprotein lipase activity and clearance rate of intravenous triglycerides after 12 months of endurance exercise training without weight loss. There were 7% to 14% decreases in the catabolic rates for HDL apolipoproteins in men with normal HDL, but not low HDL. Couillard et al[35] have suggested that the effects of exercise on low HDL-C differ depending upon whether elevated triglyceride concentrations are absent (isolated hypoalphalipoproteinemia) or present. They found that HDL-C increased after 20 weeks of endurance exercise training in the presence of elevated triglycerides, but not in its absence.

Our observations may aid the interpretation of a recent major intervention trial of men selected for their low mean HDL-C (mean ± SE, 35.8 ± 4.4 mg/dL) who failed to significantly increase their HDL-C during an exercise training program (only 1.4 ± 0.9 mg/dL after 1 year).[36] The change in HDL may have been small because the metabolic defects that gave rise to their low HDL resist change. The results of that study contrast sharply with results of 2 other trials by the same group of investigators, in which mean HDL-C significantly increased by 5.0 and 4.6 mg/dL in men having average baseline HDL-C concentrations of 41.3 and 42.5 mg/dL, respectively.[28,29] The exercise programs also produced smaller average increases in maximum aerobic capacity than the previous trials (2.7 *v* 6.5 and 5 mL/kg/min, respectively) and less average weight loss (1.1 kg loss *v* 4.6 and 3.6 kg losses, respectively). We have argued elsewhere that much of the increase in HDL-C in clinical trials of exercise can be attributed to weight loss.[37] Thus, the nonsignificant improvements in HDL-C reported in that trial may be due to a combination of factors: low initial HDL-C, modest weight loss, and small improvements in fitness.

The associations between adiposity and low HDL-C are well documented.[38,39] Our report shows that decreases in men's HDL-C associated with adiposity are different depending upon whether the HDL is high or low relative to others in the population. This finding is consistent with the observation of Katzel et al[40] that increases in HDL-C due to 10.1 kg of weight loss were positively correlated with baseline HDL-C. Whereas others report that the association between adiposity and HDL is weaker in women than men,[38,41] we observed this only for selected portions of the HDL distribution (Fig 3).

The increase in HDL-C with alcohol consumption is also well established.[17,42,43] Our analyses showed that the increase in HDL-C associated with higher alcohol intake was 3-fold greater at the 95th percentile than at the 5th of HDL in men and women. Sijbrands and Smeltb[44] reported that HDL-C increased in association with alcohol intake in hypercholesterolemic and combined hyperlipidemic patients, but not hypertriglyceridemia patients (who presumably had low HDL). However, Clevidence et al[45] did not find that baseline HDL-C significantly affected the HDL response to alcohol intake in premenopausal women.

Proof of causality requires a randomized controlled trial. Moreover, the relationships identified in this report require verification in more sedentary populations. Runners may consume diets that differ from more sedentary individuals, and interactions with diet could affect the relationships described here. The regression slopes are expected to underestimate the true slopes due to measurement error associated with the independent variables.[46] Nevertheless, our cross-sectional findings are consistent with the hypothesis that individuals with low HDL are more resistant to nonpharmacologic treatments that increase HDL than those with high HDL. Fibrate and nicotinic acid therapy both have been shown to increase HDL-C in low HDL men and to reduce coronary artery disease.[47-49] Although weight loss, vigorous exercise, and moderate alcohol intake appear to increase HDL-C, our findings suggest that a more aggressive approach may be required for the treatment of low HDL.

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