Exercise Physiology

Behavioral Versus Genetic Correlates of Lipoproteins and Adiposity in Identical Twins Discordant for Exercise

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Background—Lipoprotein and weight differences between vigorously active and sedentary monozygotic (MZ) twins were used to (1) estimate the effects of training while controlling for genotype and (2) estimate genetic concordance (ie, similarity) in the presence of divergent lifestyles.

Methods and Results—Thirty-five pairs of MZ twins (25 male, 10 female) were recruited nationally who were discordant for vigorous exercise (running distances differed by ≥40 km in male and ≥32 km in female twins). The active twins ran an average (mean±SD) of 63.0±20.4 km/wk, whereas the mostly sedentary twins averaged 7.0±13.5 km/wk. The active twins had significantly lower body mass index (difference±SE, −2.12±0.57 kg/m², P<0.0007) and significantly higher HDL cholesterol (0.14±0.04 mmol/L, P=0.004), HDL₂ (2.71±1.04 U, P=0.01), and apolipoprotein (apo) A-I (0.10±0.03 g/L, P=0.004). Despite the difference in lifestyle, when adjusted for sex, the correlations between the discordant MZ twin pairs were significant (P<0.01) for HDL cholesterol (r=0.69), apoA-I (r=0.58), and HDL₂ (r=0.67). There was no significant MZ twin correlation for body mass index (r=0.17). None of the active twins having an overweight twin were themselves overweight.

Conclusions—Behavior (vigorous exercise) may reduce genetic influences on body mass index. In contrast, genetics (or shared environment) substantially influences HDL cholesterol and HDL subclasses, even in the presence of extreme behavioral differences. There may be greater individual control over moderate degrees of obesity, whereas low HDL cholesterol may be largely predetermined and less effectively treated by vigorous exercise. (Circulation. 2005;112:350-356.)

Key Words: exercise ■ genetics ■ lipids ■ lipoproteins ■ obesity

Physical activity is recommended for the hygienic treatment of both obesity and low plasma concentrations of HDL cholesterol.¹–³ Obesity is an increasingly prevalent condition in Westernized societies that raises the risks for hypertension, type 2 diabetes, and coronary heart disease.⁴ A low HDL cholesterol value is also a risk factor for coronary heart disease and has received greater emphasis in the most recent National Cholesterol Education Program Adult Treatment Panel guidelines than in previous guidelines, reflecting its wider recognition as an important, treatable risk factor.² The relative contributions of environment and genes in determining adiposity and HDL cholesterol are pivotal in setting realistic hygienic treatment goals for individuals and populations. Specifically, a large environmental contribution would suggest the potential for successful behavioral or environmental interventions, whereas a large genetic component may suggest that these risk factors are largely predetermined.

Studies in twins suggest a substantial heritable component to obesity (or the susceptibility to obesity in permissive environments). Twin studies suggest that 60% to 90% of the variation in adiposity is genetic.⁵ Genes are estimated to account for ~70% of the variation in maximum lifetime body mass index (BMI) and adult weight gain.⁶ Plasma HDL cholesterol concentrations also appear to be influenced significantly by genes,⁷ and estimates from path analysis models suggest that the genetic heritability of HDL cholesterol is greater than its cultural heritability.⁸–¹²

Although vigorous exercise effectively increases HDL cholesterol and HDL₂,¹³ and lowers body fat,¹⁰,¹¹ its effectiveness relative to the genetic influences on these traits is unknown, nor can its effectiveness be accurately inferred from prior twin or family studies that are relevant only to the largely sedentary populations from which they were drawn. This report examines the potential for physical activity to raise HDL cholesterol and reduce weight in identical twins discordant for vigorous exercise. The sedentary twin provides an estimate of the effects of genotype on lipoproteins and body weight in the absence of exercise. It also estimates the effect of environmental factors that are shared with the active twin. By comparing the sedentary twin’s phenotype with those of the more active twin, we are able to (1) estimate the effects of training while controlling for genetic background and (2) estimate the degree of genetic similarity in the presence of divergent lifestyles.

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Methods
A divergent-twin study design was used to test for the effects of exercise while controlling for the effects of genes and shared environment by calculating the average within-twin difference in lipoproteins and BMI between a highly physically active and a more sedentary twin. The monozygotic (MZ) twins were identified from male and female participants of the National Runners’ Health Study,15,16 who reported having a living, MZ twin, 18 to 74 years old, who resided within the United States and who had no prior history of heart disease, diabetes, or cancer (except skin cancer). Zygosity was based on questionnaire responses that have been shown to be highly reliable (4% misclassification). We required weekly running distances to differ by at least 40 km (25 mi) in male and at least 32 km (20 mi) in female twins. Three weeks before a blood draw, the twins adjusted their alcohol consumption to the level of the twin whose intake was lower. We excluded twins discordant for tobacco use, medications, oral contraceptives, or postmenopausal estrogen replacement. The protocol for this study was approved by the University of California Berkeley Committee for the Protection of Human Subjects, and all participants signed the consent form approved by this committee.

As part of a telephone interview, each twin provided the name of a local clinic or hospital where it would be convenient to have their blood drawn. Blood samples were collected after a 12-hour fast and 24 hours after the most recent vigorous exercise on Mondays, Tuesdays, or Wednesdays to ensure their delivery to our laboratory by Thursday. The local clinic also measured height and weight and returned these data with the processed blood along with the signed consent form. The samples were shipped on wet ice by overnight carrier on the same day of collection and arrived at our laboratory within 18 hours.

All participants received a VHS videotape providing 16 minutes of instruction for completing the 4-day diet record; a 0- to 16-oz diet scale for weighing foods; a food record for recording food intake on Thursday, Friday, Saturday, and Sunday; and a prepaid, preaddressed envelope for returning the record. The food records were sent to the Central Dietary Data Entry Center located at Children’s Hospital Medical Center, Cincinnati, Ohio, for coding. Nutrient analyses were based on the extensive food database from the National Heart, Lung, and Blood Institute (NHBLI) nutrient assessment system used by the Lipid Research Clinics.16 Weekly running distance and participation in any other exercise were determined by questionnaires and follow-up telephone interviews.

Laboratory Measurements
The plasma samples were analyzed for concentrations of cholesterol, triglycerides, and HDL cholesterol, measured directly after precipitation of apolipoprotein (apo) B–containing lipoproteins in plasma. LDL cholesterol was calculated by subtraction of estimated VLDL and measured HDL cholesterol from the measured total cholesterol and triglycerides in plasma. Lipid assays were enzymatic end-point measurements (enzyme reagent kits from Ciba-Corning Diagnostics Corp) performed on a Ciba-Corning Express 550 automated analyzer. The measurements were standardized through the Centers for Disease Control and Prevention (CDC)–NHBLI Lipid Standardization Program. ELISAs were used for measurement of apoA-I and apoB.2 Lipid measurements were standardized through participation in the CDC–NHBLI Lipid Standardization Program. Apoprotein measurements were standardized through purchased calibration standards (Bacton Assay Systems), which were concentration-linked to the International Federation of Clinical Chemistry (IFCC) proposed Standard Reference Material, SP1, and by participation in the IFCC/CDC-directed Standardization Program. Quality control of lipid and apoprotein measurements was monitored by assay of control plasma samples run with each group of 20 or fewer test plasma samples. Coefficients of variation for the laboratory measurements were 4.9% for LDL cholesterol, 4.2% for HDL cholesterol, 2.8% for triglycerides, and 5.1% for both apoA-I and A-II.

Electrophoresis was used to determine the levels of HDL protein within 5 subclass intervals. The plasma d<1.20 g/mL fraction was obtained after single-spin ultracentrifugation (114 000g, 24 hours, 105, Beckman 50.3 rotor). Electrophoresis of HDLs in the ultracentrifuged d<1.20 g/mL fraction was done on a Pharmacia electrophoresis apparatus (GE 4-II) with slab gradient gels, as described by Blanche et al.21 After electrophoresis, plasma lipoproteins derived from ultracentrifugally isolated fractions were stained for protein content. The stained gradient gels were scanned with a model RFT densitometer (Transidyne Corp) at a wavelength of 603 nm. A mixture of 4 globular proteins (high-molecular-weight calibration kit) was run on the central lane to calibrate them for particle size. The HDL migration distances (Rf) were measured relative to the migration distance of the peak of bovine serum albumin. Differences between twins were computed for each of the 5 HDL subfractions in the total d<1.006 plasma fraction (HDLd<1.006 [1.2 to 7.8 nm diameter], HDLd<1.024 [7.8 to 8.2], HDLd<1.038 [8.2 to 8.8], HDLd<1.062 [8.8 to 9.7], and HDLd>1.062 [9.7 to 12.9]).24 The measurements were divided by 1000 for this report.

Statistical Analyses
Mean differences were evaluated by paired t test (verified nonparametrically by the sign-rank test), and correlations were assessed by Pearson correlation coefficients (verified nonparametrically by Spearman’s correlation). Linear regression was used to adjust for sex and other covariates. The average of the within-twin differences between the active and sedentary twins estimates the effects of training on lipoproteins and BMI while controlling for genetic variation (the genotype being identical within each pair) and shared environment, and the significance of the average difference tests whether an exercise effect exists independent of genotype and shared environment. The correlation between twins assesses the degree of similarity (presumably genetic, with the possible contribution of shared environment) in the presence of very divergent levels of physical activity.

Thirty-five twin pairs provide the statistical power to detect a correlation of r = 0.46 or greater and a mean difference of 0.5 SDs of the between-twin difference at 80% power, 5% significance. Exact statistical significance levels are presented in the Tables to permit adjustment for multiple hypothesis testing by Bonferroni or other techniques.

Results
Thirty-five pairs of MZ twins (10 female, 25 male) discordant for exercise participated in the study. They averaged (mean±SD) 40.5±6.8 years old. There was a 56.0±4.2 km mean difference in the average weekly running distance between twins. The active twins ran an average of 63.0±20.4 km/wk, whereas the mostly sedentary twins averaged 7.0±13.5 km/wk. There were no significant correlations for the active and more sedentary twins’ intakes of total calories (r = 0.38) or the percentage of total calories from carbohydrates (r = 0.29), fat (r = 0.10), saturated fat (r = 0.16), monounsaturated fat (r = 0.10), or polyunsaturated fat (r = 0.05). The significant twin correlation for grams of alcohol intake (r = 0.45) reflects our instruction for both twins to adjust their weekly intake to the smaller of the twin’s intake within each pair.

Table 1 displays the mean BMI and lipoprotein concentrations in the active and mostly sedentary twins and their twin-pair differences (±SE). The active twins had significantly lower BMI (P = 0.0007) and significantly higher HDL cholesterol (P = 0.004) and apoA-I (P = 0.004). There were no significant differences in the twins’ plasma apoB (P = 0.12), LDL cholesterol (P = 0.59), or triglyceride (P = 0.43) concentrations or weekly alcohol intake (difference ±SE, 15.5±16.6 mL, P = 0.36). The BMI, HDL cholesterol, and apoA-I twin-pair differences were also significant for the 25 male twin pairs considered separately. The female twin-pair differences were consistent with those of the males for HDL cholesterol, apoA-I, and BMI (presumably nonsignificant
because there were only 10 pairs). Table 2 displays the twin-pair differences for the 5 HDL subclasses as measured by gradient gel electrophoresis. The active twins had significantly higher HDL\(_2\) (0.01), specifically, significantly higher HDL\(_{3b}\) (0.004) and marginally higher HDL\(_{3c}\) (0.08). Among males, the levels of protein-stained HDL in the active twins were significantly higher for HDL\(_{3a}\) (0.004), and HDL\(_{3c}\) (0.0004), and HDL\(_{2b}\) (0.02) vis-a-vis the mostly sedentary twins.

Figures 1 and 2 compare the active twin (vertical axes) with their mostly sedentary twin (horizontal axes). The 35 plotted points represent the corresponding values of the twin pairs. The diagonal line represents the locus of equivalent values. Points fall above the diagonal when the active twins have higher values than the mostly sedentary twins and below the diagonal when the converse is true. The points lie above the diagonal (active greater than mostly sedentary) significantly more often than expected by chance for HDL cholesterol (25 above versus 10 at or below the diagonal, P=0.009 by sign test), apoA-I (23 versus 12, P=0.04), and HDL\(_2\) (27 versus 8, P=0.002). They also lie significantly more often above the diagonal for HDL\(_{3a}\) (25 versus 10, P=0.02) and HDL\(_{2b}\) (26 versus 9, P=0.006) but not HDL\(_{3b}\) (23 versus 12, P=0.09), HDL\(_{3c}\) (13 versus 22, P=0.18), or HDL\(_{3a}\) (19 versus 16, P=0.74; analyses not displayed). Figure 2 shows that the majority of points for BMI lie below the diagonal (27 versus 8, P=0.002), representing the lower BMI of the active twin.

When adjusted for sex, the correlations between the discordant MZ twin pairs were significant (P<0.01) for height (r=0.82), HDL cholesterol (r=0.69), apoA-I (r=0.58), LDL cholesterol (r=0.72), apoB (r=0.71), triglycerides (r=0.42), HDL\(_{2b}\) (r=0.52), HDL\(_{3a}\) (r=0.64), HDL\(_{3b}\) (r=0.62), and HDL\(_{3c}\) (r=0.67) but not for HDL\(_{3a}\) (r=0.19) or HDL\(_{3b}\) (r=0.20). Figure 1 shows that despite the large differences in weekly vigorous activity, HDL cholesterol, apoA-I, and HDL\(_2\) were strongly related within twin pairs. Adjustment for alcohol intake did not alter the significance of the mean differences nor the significance of the MZ twin correlations. In addition, the observed concordance does not appear to be a methodological artifact from twins being occasionally analyzed within the same batch of samples. Specifically, concordance was also demonstrated across different methodologies for measuring HDL; ie, there is a strongly significant

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**Table 1. Differences in Lipoproteins, Adiposity, and BMI in MZ Twins Discordant for Exercise**

<table>
<thead>
<tr>
<th></th>
<th>Active Twins, Mean±SD</th>
<th>Mostly Sedentary Twins, Mean±SD</th>
<th>Difference±SE</th>
<th>Significance, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male and female pairs (n=35)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>22.01±1.72</td>
<td>24.13±3.20</td>
<td>−2.12±0.57</td>
<td>0.0007</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.51±0.34</td>
<td>1.37±0.33</td>
<td>0.14±0.04</td>
<td>0.004</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.05±0.84</td>
<td>3.12±1.10</td>
<td>−0.07±0.13</td>
<td>0.59</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.94±0.46</td>
<td>1.01±0.55</td>
<td>−0.07±0.09</td>
<td>0.43</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.54±0.21</td>
<td>1.44±0.20</td>
<td>0.10±0.03</td>
<td>0.004</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>7.44±2.22</td>
<td>7.96±2.66</td>
<td>−0.52±0.32</td>
<td>0.12</td>
</tr>
<tr>
<td>Males (n=25)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>22.46±1.60</td>
<td>23.0±2.17</td>
<td>−1.54±0.49</td>
<td>0.0009</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.48±0.39</td>
<td>1.34±0.35</td>
<td>0.14±0.05</td>
<td>0.02</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.05±0.89</td>
<td>3.25±1.21</td>
<td>−0.20±0.17</td>
<td>0.24</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.96±0.51</td>
<td>1.07±0.60</td>
<td>−0.12±0.12</td>
<td>0.34</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.55±0.24</td>
<td>1.44±0.22</td>
<td>0.10±0.04</td>
<td>0.02</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>7.50±2.42</td>
<td>8.18±3.01</td>
<td>−0.69±0.42</td>
<td>0.12</td>
</tr>
<tr>
<td>Females (n=10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m(^2)</td>
<td>20.89±1.57</td>
<td>23.7±5.09</td>
<td>−2.82±1.61</td>
<td>0.11</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.59±0.21</td>
<td>1.47±0.25</td>
<td>0.11±0.08</td>
<td>0.17</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>3.06±0.73</td>
<td>2.80±0.68</td>
<td>0.26±0.14</td>
<td>0.09</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.89±0.34</td>
<td>0.86±0.39</td>
<td>0.04±0.10</td>
<td>0.72</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.53±0.14</td>
<td>1.44±0.15</td>
<td>0.09±0.05</td>
<td>0.12</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>7.29±1.72</td>
<td>7.39±1.44</td>
<td>−0.10±0.41</td>
<td>0.82</td>
</tr>
</tbody>
</table>

**Table 2. Differences (± SE) in Protein-Stained HDL Total Subclass Intervals in MZ Twins Discordant for Exercise**

<table>
<thead>
<tr>
<th>Subclass</th>
<th>Females</th>
<th>Males</th>
<th>Significance, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL(_{2a}) (area)</td>
<td>0.04±0.18</td>
<td>−0.19±0.22</td>
<td>−0.13±0.16</td>
</tr>
<tr>
<td>HDL(_{2b}) (area)</td>
<td>−0.09±0.44</td>
<td>0.41±0.28</td>
<td>−0.32±0.24</td>
</tr>
<tr>
<td>HDL(_{2c}) (area)</td>
<td>−0.66±1.22</td>
<td>1.35±0.46</td>
<td>0.77±0.49</td>
</tr>
<tr>
<td>HDL(_{3a}) (area)</td>
<td>0.26±1.13</td>
<td>1.95±0.47</td>
<td>1.46±0.47</td>
</tr>
<tr>
<td>HDL(_{3b}) (area)</td>
<td>−0.77±1.18</td>
<td>2.06±0.80</td>
<td>1.25±0.69</td>
</tr>
<tr>
<td>HDL(_{3c}) (area)</td>
<td>−0.51±2.12</td>
<td>4.00±1.12</td>
<td>2.71±1.04</td>
</tr>
</tbody>
</table>

Significance levels are as follows: *P<0.05, †P<0.01, ‡P<0.005, §P<0.001.
- 1.6 kg/m², \(P = 0.06\)). This difference was particularly strong among males (−2.6 kg/m², \(P = 0.02\)). This suggests that those active twins having an overweight twin had historically lost more weight (presumably due to running) than those not having an overweight twin.

The mostly sedentary twins included 25 sedentary pairs (9 female, 16 male) who did not run at all or engage in other vigorous activity (mean ±SD, 55.9±12.7 km/wk less than their active twin). Results similar to the complete sample were obtained when the analyses were restricted to this subset of twin pairs. The active twin weighed significantly less than the sedentary twin (difference ±SE: −1.93 ±0.74 kg/m²) and had significantly higher HDL cholesterol (difference ±SE, 0.14 ±0.05 mmol/L, \(P = 0.005\)), apoA-I (0.09 ±0.04 g/L, \(P = 0.02\)), HDL₃a (3.16 ±1.17 U, \(P = 0.01\)), HDL₃b (1.51 ±0.61 U, \(P = 0.02\)), and HDL₃c (1.64 ±0.65 U, \(P = 0.02\)). There were no significant differences for plasma LDL cholesterol (−0.08 ±0.14 mmol/L, \(P = 0.56\)), triglycerides (−0.07 ±0.05 mmol/L, \(P = 0.16\)), apoB (−0.39 ±0.29 mmol/L, \(P = 0.19\)), HDL₃a (0.04 ±0.15 U, \(P = 0.80\)), HDL₃b (−0.32 ±0.26 U, \(P = 0.22\)), or HDL₃c (0.69 ±0.65 U, \(P = 0.30\)). Table 3 presents the means for the active and sedentary twins and their differences by sex. The active male twins had significantly lower BMI and significantly higher HDL cholesterol than their sedentary twin and marginally higher apoA-I. When adjusted for sex, the correlations between the discordant MZ pairs were significant (\(P < 0.01\)) for height (\(r = 0.78\)), HDL cholesterol (\(r = 0.66\)), apoA-I (\(r = 0.52\)), LDL cholesterol (\(r = 0.85\)), apoB (\(r = 0.83\)), triglycerides (\(r = 0.77\)), HDL₃a (\(r = 0.60\)), HDL₃b (\(r = 0.54\)), HDL₃c (\(r = 0.72\)), and HDL₄ (\(r = 0.65\)) but not for HDL₃ (\(r = 0.38\)), HDL₄ (\(r = 0.05\)), or BMI (\(r = 0.15\)).

**Discussion**

These results suggest that behavior (vigorous exercise) can mitigate genetic influences on BMI. In contrast, genetics (or shared environment) substantially influences plasma HDL concentrations even in the presence of extreme behavioral differences. The prescription of vigorous exercise to reduce weight is likely to be much more effective than the prescription of vigorous exercise to raise HDL cholesterol. The public health promotion of vigorous exercise may be far more successful when body weight is targeted rather than HDL cholesterol. Our results suggest that there may be individual correlation between the active twins’ protein-stained HDL₂ from gradient gel electrophoresis and the mostly sedentary twins’ HDL cholesterol that was estimated by precipitation (\(r = 0.69\)) and between the active twins’ HDL cholesterol and the mostly sedentary twins’ protein-stained HDL₂ (\(r = 0.67\)).

We found no significant MZ twin correlation for BMI (Figure 2). Thirteen of the mostly sedentary twins were moderately overweight (BMI >25 kg/m²), compared with only 2 of the active twins. None of the active twins having an overweight twin were themselves overweight. The twins provided data on their greatest lifetime weight, which was used to estimate the effect of exercise, because under sedentary conditions, individuals are expected to gain weight as they age. The reduction in BMI from the time of greatest lifetime weight was greater in those active twins with an overweight twin than in those with a lean twin (difference,
control over moderate degrees of obesity, whereas low HDL cholesterol levels may be largely predetermined and less effectively treated by vigorous exercise. These analyses do not preclude the possibility that within the population, there may be a minority of individuals for whom weight is primarily genetic or HDL cholesterol is susceptible to intervention.

The strong correlations that were observed for HDL cholesterol, apoA-I (the major apolipoprotein of HDL), and HDL2 (the lighter, larger fraction of HDL) are consistent with the high level of heritability reported by others on presumably mostly sedentary populations. These included estimates of genetic heritability from twin and pedigree studies for HDL cholesterol (35%, 34%, 34%, 59%, 26%, 66%, 27 and 74% of HDL variation), HDL2 cholesterol (37% and 50%), and apoA-I (50% to 58% and 66%). In contrast, the absence of any significant association in adiposity between the running and the sedentary twin was unexpected. Prior studies of twins (presumably mostly sedentary) revealed heritability estimates that ranged from 0.6 to 0.9. More than 300 genes, markers, and chromosomal regions have been related to adiposity or weight. Shared environmental influences do not appear to explain the strong correlation of adiposity in MZ twins. Specifically, adoption studies showed little concordance between parents’ and their adoptive children’s adiposity, and studies of MZ twins raised apart suggest that the shared environments within families may have less influence on BMI than genes.

Our findings are qualitatively consistent with prior cross-sectional studies that showed that male and female runners have higher plasma HDL cholesterol concentrations and lower body weight than do sedentary men and women. The higher HDL cholesterol reflects higher plasma concentrations of the larger particles (HDL2b, HDL2a, or HDL3a subclasses). These lipoprotein and weight differences may explain in part the lower risks of cardiovascular disease and total mortality in physically active and cardiovascularly fit men and women compared with those who are inactive and unfit. Differences in LDL cholesterol and triglycerides did not achieve statistical significance between the active and sedentary twins. This is contrasts with several cross-sectional and intervention studies that suggested that running decreases plasma triglyceride and LDL cholesterol concentrations in men but not necessarily in women.

Particularly in men, the more physically active twin had higher plasma levels of HDL3a and HDL2, (including both HDL2b and HDL2a). Despite the differences in activity, plasma levels of HDL3a, HDL2a, and HDL2b were correlated significantly between the active and the more sedentary twin. These differences and associations reflect 2 overlapping HDL particle distributions that differ in their apolipoprotein compositions: HDL containing both apoA-I and apoA-II, which includes major components within HDL3a, HDL3a, and HDL2b subclasses, and HDL containing apoA-I and no apoa-II, with major components within the HDL3a, HDL3a, and HDL2b subclasses. The 2 HDL distributions have minimal exchange of their apoA-I, and metabolic interconversions between HDL subclasses appear to occur predominantly within each distribution.

The present analyses suggest that HDL cholesterol increased by 0.10 mg/dL per kilometer run (5.5-mg/dL HDL cholesterol difference divided by a 57.4-km difference in weekly distance run). Elsewhere, we reported that experimental 1-year training was reported to increase HDL cholesterol by 1.4 mg/dL in men who averaged 13.9 km/wk, or 0.10 mg/dL per kilometer run. Both designs controlled for genetic effects (ie, the genotype being constant for both MZ twins and experimentally induced changes within an individual) and yielded consistent estimates. The mean HDL cholesterol difference between active and sedentary female MZ twins was 4.40 mg/dL. On the basis of the 45.4-km/wk difference in their running distance, we estimate that HDL increased by 0.10 mg/dL per km/wk run, which is consistent with the prior 2 estimates.
The aforementioned estimates are lower than our previous cross-sectional estimates of the increase in HDL in men (0.14 mg/dL per kilometer run) and women (0.13 mg/dL per kilometer run). Unlike comparisons of twins or training studies, cross-sectional studies contrast individuals of differing exercise levels and genetic profiles and may therefore overestimate the HDL change per kilometer run when runners are self-selected, because genes affect both the propensity to exercise and high HDL cholesterol. Thompson and Rader summarized data from ourselves, the Health, Risk Factors, Exercise Training, and Genetics (HERITAGE) Family Study, and others showing that higher baseline HDL cholesterol levels predict a larger HDL training response. Several genes are purported to affect the lipoprotein responses to exercise training, including apoE, endothelial lipase, and cholesteryl ester transfer protein. We have demonstrated in 2 separate training studies that sedentary men who have higher HDL cholesterol at baseline will run longer weekly distances by the end of a training program compared with men who begin with low HDL. Higher baseline HDL cholesterol may identify individuals with muscle fiber types or the ability to deliver fatty acids to muscle energy that facilitates running. The high HDL cholesterol levels of the sedentary twins (50.6 mg/dL, Table 3) suggest that just the ability to run (as represented by their more active brothers) genetically confers high HDL cholesterol.

Theoretically, randomized, controlled clinical trials should provide the most definitive proof that increasing physical activity causes HDL cholesterol to increase and body weight to decrease. In practice, however, the levels of exercise achieved in training studies scarcely ever approach the exercise differential observed cross-sectionally. The HERITAGE family study of 650 men and women produced small increases in HDL cholesterol (1.1 mg/dL in men and 1.4 mg/dL in women) and small decreases in weight (0.9 lb in men and 0.4 lb in women) after 20 weeks of training. In another study, 1 year of training was reported to increase HDL cholesterol by 1.4 mg/dL in men who averaged 13.9 km/wk.

In summary, the discordant-twin study design provides the advantages of both cross-sectional association studies (large phenotypic effects) and training studies (controlling for genotype) without the self-selection bias of cross-sectional association studies or the small phenotypic response of training studies. The design yields estimates of the increase in HDL cholesterol per kilometer run per week that agrees very well with those derived experimentally and shows that the projected benefits are likely to accrue beyond the limited training distances that can usually be achieved experimentally. HDL cholesterol, apoA-I, HDL3a, and HDL2 (including HDL2a and HDL2b) all appear to increase with exercise. However, genetic influences appear to be a greater determinant of HDL levels than exercise, and the large differences in HDL cholesterol between sedentary men and runners are likely to be due in large part to genetic differences between runners and nonrunners. Merely sharing the same genes appears sufficient to bestow a desirable level of HDL cholesterol in the absence of activity. This can be further improved by the addition of vigorous activity.

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References


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