Effects of Exercise-induced Weight Loss on Low Density Lipoprotein Subfractions in Healthy Men


One-year changes in low density lipoprotein (LDL) peak flotation (Sf) rate and serum mass concentrations of LDL of Sf 0 to 7 (small LDL), LDL of Sf 7 to 12 (large LDL), Intermediate density lipoprotein (IDL) of Sf 12 to 20, and very low density lipoprotein (VLDL) of Sf 20 to 400 were compared between men assigned at random to a 1-year exercise program (N=48) or to a sedentary control condition (N=31). Distance run among exercisers varied substantially (mean ± SD: 12.7 ± 8.9 km/week). Mean changes were not significantly different between the exercise and control groups for any of the low to very low density lipoprotein measurements. However, within the exercise group: 1) distance run correlated negatively with changes in the mass concentrations of small LDL; and 2) weight loss and reduced upper body obesity correlated positively with changes in small LDL, IDL, and VLDL mass and negatively with change in LDL peak flotation rate. Analyses with partial correlations suggest that weight loss may primarily affect LDL mass distributions through metabolic processes associated with high density lipoprotein, or small VLDL (Sf 20 to 60). The decrease in small LDL concentrations and the increase in LDL peak flotation rate suggest that exercise-induced weight loss may be effective in reducing coronary heart disease risk in persons genetically predisposed to a high-risk lipoprotein profile. (Arteriosclerosis 9:623–632, September/October 1989)

Numerous studies have shown that running increases concentrations of plasma high density lipoproteins (HDL), and particularly the HDL₃ subclass. However, the effects of running on low density lipoproteins (LDL) and LDL subclasses have not been clearly established. Several studies link high serum concentrations of smaller, denser LDL particles with coronary heart disease. Increased concentrations of small LDL were associated with coronary disease progression in the National Heart, Lung, and Blood Institute Type II Coronary Intervention Study. In another study, there were higher concentrations of small LDL in patients with premature coronary heart disease. The increased concentrations of small LDL were associated with a higher risk of coronary heart disease than in matched controls. There is also a predominance of small, dense LDL particles in patients with familial combined hyperlipidemia.

We have shown in a previous cross-sectional study that runners have lower serum concentrations of small LDL particles of flotation rate (Sf) 0 to 7 and very low density lipoprotein (VLDL) particles of Sf 20 to 400 than non-runners. Although not originally reported, LDL peak flotation rate was also higher in the runners (mean ± SD: 6.68 ± 0.94 Sf) than in the sedentary men (5.72 ± 0.86 Sf, p<0.005). Alone, these cross-sectional observations do not distinguish lipoprotein changes due to exercise from lipoprotein differences due to self-selection. For example, there may be a tendency for men who have higher HDL cholesterol and lower triglyceride concentrations in plasma to take up running as a sport.

We have previously shown that HDL cholesterol and LDL₃ mass concentrations increased in association with exercise-induced weight loss in men who participated in a 1-year running program. The present report compares the 1-year changes in LDL and VLDL subfraction concentrations between the runners and sedentary controls. We also examine lipoprotein changes within the exercise group to address the following issues: 1) Does distance run, improved fitness, weight loss, or regional adiposity change affect specific particle subpopulations within the low to very low density spectrum as suggested by cross-sectional data? 2) Are changes in LDL during exercise and weight loss associated with changes in HDL or VLDL subclasses? 3) What are the implications of measurement precision (i.e., our ability to estimate an individual’s true weight, body composition, regional adiposity, and lipoprotein levels) in regard to the interpretation of correlations between changes in these variables?

Methods

Subjects and Laboratory Measurements

Eighty-one sedentary men, ages 30 to 55 years, were assigned at random to either a supervised running group of 48 persons or to a sedentary control group of...
and reported caloric intake in 34 exercisers who did not report going on special diets to lose weight and four exercisers who reported going on special diets to lose weight. The smoothed scatterplot corresponds to the nondieting exercisers only. Weight loss corresponds to increased caloric intake in the nondieting exercisers and to a decrease in caloric intake in the exercisers who dieted.

33 persons and were followed up for 1 year. Those assigned to the exercise group were encouraged to run 5 days a week, 45 minutes per day after 6 weeks, while those assigned to the control group were asked to remain sedentary throughout the year. Laboratory measurements were taken at baseline and after 3, 6, 9, and 12 months (the 1-year data appear in the present report). Waist girths were measured as the horizontal circumference at the umbilicus, and hip and thigh girths were measured as the largest horizontal circumference around the buttocks and thigh with standard cloth tapes. Body compositions were estimated from hydrostatic weighing, caloric intakes were calculated from 3-day diet records, and maximal oxygen uptakes (VO_{2\max}) were determined from treadmill tests to exhaustion. Averages for distance run per week were obtained from diaries maintained by the runners. Lipoproteins were measured by analytic ultracentrifugation of fasting serum samples, and concentrations of total lipoprotein mass were estimated by using computer techniques for HDL\textsubscript{2} (flotation rate F1 1.20 3.5 to 9), HDL\textsubscript{3} (F1 1.00 0 to 3.5), small LDL (S, 0 to 7), large LDL (S, 7 to 12), intermediate density lipoprotein (IDL) (S, 12 to 20), small VLDL (S, 20 to 60), and large VLDL (S, 60 to 400) mass concentrations, and changes in the mode of the LDL particle distribution (LDL peak flotation rate). Fasting lipoprotein cholesterol concentrations were determined by the methods of the Lipid Research Clinics.

The majority of the exercisers who lost weight did so by running rather than by dieting. The smooth scatterplot of Figure 1 shows that total weight loss corresponded to increased caloric intake in the nondieting exercisers. They lost an average of 2.4 kg/1000 additional kilocalories consumed. However, there were also five men who reported on their diet records that they had dieted to lose weight in addition to exercise. In contrast to the nondieting exercisers, weight loss in the dieting exercisers was associated with a decrease in caloric intake. Analyses were therefore performed with the dieters both included and excluded. Correlations are presented for all exercisers when consistent results are obtained for both dieters and nondieters and for nondieters only when it was clear that including dieters confounded the results for the nondieters (i.e., distance run).

**Statistics**

The differences between the exercise and control groups were evaluated by using the significance levels assigned by Wilcoxon's two-sample sign rank test. Pearson correlation coefficients and linear regression were used to assess pairwise associations. Standard significance levels and confidence intervals were verified by permutation tests and bootstrap resampling procedures, respectively. The linear relationships between lipoprotein concentrations and other variables were verified by the scatterplot smoothing procedure described by Cleveland, with three-fourths of the observations used to estimate each fitted point.

**Results**

**Group Differences at Baseline and after One Year of Intervention**

Two exercisers and three control subjects were missing lipoprotein mass measurements at 1 year. The remaining 46 exercisers and 30 controls were not significantly different for serum mass concentrations of small LDL, large LDL, IDL, small VLDL, and LDL peak flotation rate. Exercisers tended to have lower concentrations of large VLDL than controls at baseline (38.9 ± 5.7 vs. 62.1 ± 8.9 mg/dl, p=0.06). Upper-body obesity, as measured by the ratio of the waist girth to the hip girth (× 100), was initially lower in exercisers than in controls (91.5 ± 0.7 vs. 93.9 ± 0.8, p=0.03). As previously reported, the treatment and control groups were also well matched at baseline for VO\textsubscript{2\max}, lean mass, fat mass, and total body mass.

The exercise group ran an average of 12.7 km/week between the 5th and 12th month. Table 1 shows that this level of exercise produced significant mean increases in VO\textsubscript{2\max} and significant mean reductions in fat and total body mass and upper body obesity in exercisers relative to controls. However, this level of exercise did not produce significant mean differences in the mass concentrations of small LDL (p=0.15), large LDL (p=0.56), IDL (p=0.39), small VLDL (p=0.32), large VLDL (p=0.93), and LDL peak flotation rate (p=0.34) between exercisers and controls. Analyses henceforth include exercisers only.

**Changes in Weight and Lipoprotein Subfraction Concentrations**

One-year changes in total body mass were positively correlated with changes in small LDL, IDL, and small VLDL concentrations and negatively correlated with peak LDL flotation rate (Table 2). Changes in the ratio of waist girth to hip girth also correlated with these lipoprotein changes.
Table 1. Adiposity, Calorie Intake, Fitness, Serum Lipoprotein Mass Concentrations, and LDL Peak Flotation Rate in Exercisers and Controls

<table>
<thead>
<tr>
<th></th>
<th>Baseline everyone (mean±SD)</th>
<th>Change after 1 year (mean±SD)</th>
<th>Exercisers – controls (difference±SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calorie intake (kcal/day)</td>
<td>2485.7±586.2</td>
<td>−181.9±682.7</td>
<td>129±160.2</td>
</tr>
<tr>
<td>Total body mass (kg)</td>
<td>77.1±10.3</td>
<td>−1.9±3.8</td>
<td>0.6±3.9</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>60.2±7.4</td>
<td>−0.2±2.2</td>
<td>1.4±2.5</td>
</tr>
<tr>
<td>Fat body mass (kg)</td>
<td>16.9±5.7</td>
<td>−1.9±3.5</td>
<td>1.9±4.1</td>
</tr>
<tr>
<td>Abdominal skinfold (mm)</td>
<td>29.3±11.6</td>
<td>−5.3±8.2</td>
<td>−0.2±6.1</td>
</tr>
<tr>
<td>Abdominal girth (cm)</td>
<td>92.5±8.5</td>
<td>−3.0±3.7</td>
<td>−0.1±3.5</td>
</tr>
<tr>
<td>Thigh skinfold (mm)</td>
<td>16.6±6.1</td>
<td>−3.1±4.2</td>
<td>−0.4±3.5</td>
</tr>
<tr>
<td>Thigh girth (cm)</td>
<td>56.5±3.9</td>
<td>−1.9±1.9</td>
<td>−1.0±2.6</td>
</tr>
<tr>
<td>Waist-to-hip girth ratio</td>
<td>92.5±4.7</td>
<td>−1.3±2.1</td>
<td>0.2±2.0</td>
</tr>
<tr>
<td>VOₐₓ max (ml/kg/min)</td>
<td>34.9±6.3</td>
<td>7.5±8.4</td>
<td>−1.4±4.1</td>
</tr>
<tr>
<td>Serum mass concentrations (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small LDL (S&lt;sub&gt;0–7&lt;/sub&gt;)</td>
<td>227.8±65.3</td>
<td>−8.6±53.4</td>
<td>8.2±38.4</td>
</tr>
<tr>
<td>Large LDL (S&lt;sub&gt;7–12&lt;/sub&gt;)</td>
<td>132.3±41.9</td>
<td>10.5±39.5</td>
<td>14.7±40.0</td>
</tr>
<tr>
<td>IDL (S&lt;sub&gt;12–20&lt;/sub&gt;)</td>
<td>42.2±18.8</td>
<td>0.1±14.9</td>
<td>3.9±14.4</td>
</tr>
<tr>
<td>Small VLDL (S&lt;sub&gt;20–60&lt;/sub&gt;)</td>
<td>53.4±29.6</td>
<td>5.6±21.8</td>
<td>14.2±26.8</td>
</tr>
<tr>
<td>Large VLDL (S&lt;sub&gt;60–400&lt;/sub&gt;)</td>
<td>48.4±43.1</td>
<td>3.1±32.8</td>
<td>3.7±43.4</td>
</tr>
<tr>
<td>LDL peak flotation rate</td>
<td>5.9±0.9</td>
<td>0.1±0.7</td>
<td>0.0±0.6</td>
</tr>
</tbody>
</table>

Of the 46 exercisers and 32 controls with complete data on lipoprotein subfraction mass concentrations at baseline and 1 year, additional data were obtained on 45 exercisers and 32 controls for LDL peak flotation rate, 43 exercisers and 30 controls for total body mass (weight), 40 exercisers and 30 controls for body composition (lean and fat body mass), 35 exercisers and 29 controls for waist-to-hip girth ratio, 38 exercisers and 27 controls for VO₂max, and 38 exercisers and 26 controls for total caloric intake.

Significance levels from Wilcoxon two-sample tests are: *p<0.05; †p<0.01; and ‡p<0.0001.

LDL=low density lipoprotein, IDL=intermediate density lipoprotein, VLDL=very low density lipoprotein, VO₂max=maximal oxygen uptake.

Table 2. Correlations for Distance Run per Week and Changes in Body Composition and Caloric Intake versus Changes in Plasma Mass Concentrations of LDL to VLDL and LDL Peak Flotation Rate during 1 Year of Exercise Training

<table>
<thead>
<tr>
<th></th>
<th>Distance run per week</th>
<th>Δ total body mass</th>
<th>Δ fat body mass</th>
<th>Δ lean body mass</th>
<th>Δ LDL peak flotation rate (Sₐ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ small LDL (S&lt;sub&gt;0–7&lt;/sub&gt;)</td>
<td>−0.35*</td>
<td>0.43†</td>
<td>0.46‡</td>
<td>0.02</td>
<td>0.45†</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.58,−0.06)</td>
<td>(0.21,0.64)</td>
<td>(0.30,0.63)</td>
<td>(−0.31,0.36)</td>
<td>(0.19,0.68)</td>
</tr>
<tr>
<td>Δ large LDL (S&lt;sub&gt;7–12&lt;/sub&gt;)</td>
<td>0.11</td>
<td>−0.15</td>
<td>−0.04</td>
<td>−0.22</td>
<td>−0.23</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.15,0.39)</td>
<td>(−0.58,0.24)</td>
<td>(−0.48,0.34)</td>
<td>(−0.60,0.17)</td>
<td>(−0.48,0.08)</td>
</tr>
<tr>
<td>Δ IDL (S&lt;sub&gt;12–20&lt;/sub&gt;)</td>
<td>−0.17</td>
<td>0.35*</td>
<td>0.24</td>
<td>0.23</td>
<td>0.34*</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.38,0.07)</td>
<td>(0.10,0.57)</td>
<td>(0.01,0.46)</td>
<td>(0.01,0.47)</td>
<td>(0.06,0.56)</td>
</tr>
<tr>
<td>Δ small VLDL (S&lt;sub&gt;20–60&lt;/sub&gt;)</td>
<td>−0.20</td>
<td>0.66‡</td>
<td>0.56‡</td>
<td>0.26</td>
<td>0.39*</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.47,0.08)</td>
<td>(0.50,0.78)</td>
<td>(0.34,0.72)</td>
<td>(−0.04,0.52)</td>
<td>(0.14,0.64)</td>
</tr>
<tr>
<td>Δ large VLDL (S&lt;sub&gt;60–400&lt;/sub&gt;)</td>
<td>−0.10</td>
<td>0.38*</td>
<td>0.23†</td>
<td>0.28</td>
<td>0.37†</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.41,0.16)</td>
<td>(0.11,0.57)</td>
<td>(−0.06,0.46)</td>
<td>(−0.03,0.51)</td>
<td>(0.10,0.60)</td>
</tr>
<tr>
<td>Δ LDL peak flotation rate (Sₐ)</td>
<td>0.22</td>
<td>−0.50±</td>
<td>−0.42†</td>
<td>−0.22</td>
<td>−0.48†</td>
</tr>
<tr>
<td>95% confidence interval</td>
<td>(−0.09,0.47)</td>
<td>(−0.71,−0.24)</td>
<td>(−0.59,−0.17)</td>
<td>(−0.52,0.06)</td>
<td>(−0.68,−0.19)</td>
</tr>
</tbody>
</table>

Sample size 41 43 40 40 39

Significance levels from 1000 permutations are: *p<0.05; †p<0.01; ‡p<0.001.

See Table 1 for a list of abbreviations.

Men who reported dieting are excluded from the correlations for distance run.

Figure 2 shows that changes in serum mass concentrations of small LDL, small VLDL, and HDL₂ were similar for men who lost weight by running without caloric restriction and men who lost weight by both caloric restriction and running. The scatterplot smoothing procedure shows that the relationships between changes in total body mass and these lipoproteins were essentially linear. Changes in small LDL concentrations, small VLDL concentrations, and LDL peak flotation rate occurred primarily in association with fat body mass change, not lean body mass change (Ta-
Interrelationships of Lipoprotein Subfractions and Total Weight Loss

There were 42 exercisers with complete data for HDL, LDL, and body weight at baseline and 1 year. In these men, changes in HDL concentrations correlated negatively with changes in small LDL concentrations, positively with LDL peak flotation rate, and negatively with total body mass (Figure 3). Adjustment for HDL change essentially eliminated all associations between changes in total body mass and small LDL concentrations (from r=0.42 to r=0.07) and LDL peak flotation rate (from r=−0.50 to r=−0.04). Changes in small VLDL concentrations also correlated strongly with changes in small LDL, LDL peak flotation rate, and total body mass in these men (Figure 3). Adjustment for small VLDL change also substantially reduced the association between changes in total body mass and small LDL (from r=0.42 to r=0.11) and LDL peak flotation rate (from r=−0.50 to r=−0.10).

Figure 2. Relationship of 1-year changes in serum mass concentrations of high density lipoprotein (HDL), small, low density lipoprotein (LDL) particles (Sf 2 to 6), and small, very low density lipoprotein (VLDL) particles (Sf 20 to 60) to change in total body mass in dieting and nondieting exercisers. The smoothed scatterplot includes both dieting and nondieting exercisers.

Distance run per week correlated significantly with loss of total weight (r=−0.30) and fat body mass (r=−0.32), improved maximum aerobic capacity (ΔVO₂max, r=0.47) and correlated with increases in HDL among nondieting exercisers.6,7,8 But changes in IDL, total VLDL concentrations, and LDL peak flotation rate were not significantly related to distance run despite their significant correlation with exercise-induced weight loss. The average distance run per week did correlate significantly and inversely with changes in small LDL concentrations among nondieting exercisers (Table 2). This may reflect the coordinate relationship between HDL and small LDL since the correlation between distance run per week and Δ small LDL became nonsignificant when adjusted for Δ HDL, as did the correlation between Δ HDL and distance run when adjusted for Δ small LDL concentrations. Change in VO₂max did not correlate significantly with Δ small LDL (r=0.07), Δ large LDL (r=−0.17), Δ IDL (r=0.12), Δ small
Among exercisers, serum concentrations of small LDL, IDL, and VLDL decreased and LDL peak flotation rate increased in association with weight loss and reduced upper body obesity. Serum small LDL concentrations also decreased in association with distance run. These findings should be interpreted with caution because they were derived from the examination of a larger number of correlations (see Table 2), thereby increasing the probability of a type I error for simultaneous inference. Nevertheless, these relationships are consistent with differences observed cross-sectionally when lean long-distance runners were compared to less lean sedentary men.5

Change in large LDL may have shown no significant relationships with distance run and weight loss because measurements of large LDL are less reproducible than those for small LDL (see Appendix). Large LDL may be more variable over repeated measurements because there may be a greater number of metabolic parameters affecting large LDL levels, including rate of synthesis from LDL precursors (small VLDL and IDL), rate of conversion to small LDL, rate of uptake by hepatic receptors, and rate of exchange of large LDL between the vascular and extravascular spaces.15 Larger, more buoyant LDL particles may also have a shorter residence time in the plasma than smaller, more dense LDL.16,17 Because of these factors, serum concentrations of large LDL may be more sensitive to short-term metabolic perturbations than are concentrations of small LDL particles.

Weight loss correlated more strongly with changes in small VLDL of S, 20 to 60 than with changes in large VLDL of Sf 60 to 400. The low correlations for large VLDL may be the consequence of the greater variability in the large VLDL measurement (Appendix). Alternatively, weight loss may selectively reduce S, 20 to 60 lipoprotein mass. Large and small VLDL particles follow different metabolic pathways.18 Small VLDL particles are the primary precursors of LDL and IDL, while large VLDL particles are usually cleared directly as remnant particles without first becoming LDL.19 The large VLDL remnants also reside within the S, 20 to 60 flotation range until they are cleared.20 Therefore, the observed reductions in S, 20 to 60 lipoprotein mass during weight loss and exercise may be the result of accelerated catabolism or clearance of large VLDL remnants or reduced small VLDL production.

Discussion

Among exercisers, serum concentrations of small LDL, IDL, and VLDL decreased and LDL peak flotation rate increased in association with weight loss and reduced upper body obesity. Serum small LDL concentrations also decreased in association with distance run. These findings should be interpreted with caution because they were derived from the examination of a larger number of correlations (see Table 2), thereby increasing the probability of a type I error for simultaneous inference. Nevertheless, these relationships are consistent with differences observed cross-sectionally when lean long-distance runners were compared to less lean sedentary men.5

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Interrelationships between Lipoprotein Subfraction Changes

Changes in small LDL, LDL peak flotation rate, HDL2, and small VLDL during weight loss were highly correlated (Figure 3). However, changes in LDL were no longer correlated with weight loss when adjusted for changes in HDL2 and VLDL. These correlations could be explained by decreased cholesteryl ester-triglyceride exchange between lipoproteins, brought about by reductions in plasma VLDL concentrations and postprandial lipemia during weight loss.21,22

Pathway of High Cholesteryl Ester-Triglyceride Exchange

This pathway may inhibit the formation of HDL2 and promote the formation of small LDL.21,22 Cholesteryl ester,
Figure 4. Distribution of lipoprotein mass concentration (vertical axes) by flotation rate (horizontal axes) for high density lipoprotein (HDL) (column 1) and low density lipoprotein (LDL) (column 2) at baseline and 1 year later in the six exercisers who had the greatest total weight loss. Also displayed are the changes in the mass concentrations of HDL (column 3) and LDL (column 4) between baseline and 1 year in these men. Changes in HDL mass \( F_{1,20} \) 3.5 to 9 and small LDL mass \( S_f \) 0 to 7 are designated by the shaded portions of the difference plots in columns 3 and 4.
formed from free cholesterol by lecithin:cholesterol acyltransferase (LCAT), is incorporated into the HDL core. HDL may then form a ternary complex with cholesteryl ester transfer protein and either chylomicron or VLDL. When this occurs, the cholesteryl ester transfer protein may mediate the net transfer of cholesteryl ester from HDL to the chylomicron or VLDL particle. In exchange for the cholesteryl ester, triglyceride is transferred to HDL, which may then be hydrolyzed by hepatic lipase. In this way, cholesteryl ester-triglyceride exchange may prevent the accumulation of cholesteryl ester in HDL, which could lead to the formation of HDL3. Cholesteryl ester transfer protein may also mediate the exchange of LDL cholesteryl ester for chylomicron triglycerides or VLDL triglycerides. This could yield triglyceride-enriched LDL particles, which when hydrolyzed by lipase, become smaller, denser LDL particles. It is also possible that cholesteryl ester-triglyceride exchange may promote the synthesis of a triglyceride-enriched form of LDL that yields small LDL particles after lipolysis.

**Pathway of Low Cholesteryl Ester-Triglyceride Exchange**

This pathway is hypothesized to promote the formation of HDL2 and inhibit the formation of small LDL. Specifically, HDL2 concentrations may increase when cholesteryl ester is accumulated in HDL, and small LDL concentrations may decrease when the triglyceride-enriched IDL or LDL precursors of small LDL do not form. This may lead to a predominance of larger LDL particles, corresponding to a higher LDL peak flotation rate.

Weight loss may favor the pathway of low cholesteryl ester-triglyceride exchange, thereby increasing HDL2 concentrations, decreasing small LDL concentrations, and increasing LDL peak flotation rate. In vivo studies suggest that cholesteryl ester-triglyceride exchange is limited by the size of the pool of triglyceride-rich lipoprotein particles. Running and weight loss each decrease nonfasting triglycerides (primarily in chylomicrons) and fasting triglycerides (primarily in VLDL). Serum VLDL concentrations may indirectly measure the size of the triglyceride-rich lipoprotein pool in the fasting and postprandial states. This may explain why changes in serum VLDL concentrations correlate negatively with changes in HDL2 and LDL peak flotation rate and positively with changes in small LDL concentrations during weight loss (Figure 3).

Cholesteryl ester-triglyceride exchange could also be reduced by exercise and weight loss through factors other than decreased availability of acceptor particles. Reduced exchange could occur because the ratio of free cholesterol to phospholipids on the lipoprotein surfaces is reduced. Exercise and weight loss each decrease fasting free fatty acid concentrations, which could inhibit the binding of cholesteryl ester transfer protein to lipoproteins and reduce lipid transfer associated with VLDL-LDL complex formation. The low fasting free fatty acid levels of runners are probably the consequence of their reduced adiposity; the release of free fatty acids from adipose tissue increases linearly with the size of the fat cell, and basal lipolysis decreases in relation to decreasing fat cell size during weight loss.

**Bias due to Errors In Measuring Body Composition**

Table 2 shows that the changes in LDL concentrations correlated equally well with changes in the ratio of waist girth to hip girth, total weight, and fat body mass. These results are in apparent conflict with the report by Terry et al., which showed that small LDL, IDL, and total VLDL mass concentrations correlated more strongly with the waist-to-hip girth ratio than with other measures of adiposity in the same 72 men studied cross-sectionally at baseline.

The apparent discrepancy between our findings and those reported by Terry et al. can be resolved when the effects of measurement error bias are compared for the two study designs. When regional adiposity, body composition, and total body mass are measured imprecisely (i.e., with error), their correlations will underestimate the true correlations. The bias due to measurement error is expected to be greater for longitudinal studies than for cross-sectional data. Measurement error contributes twice to the total variance for change data because measurement error is accrued at both baseline and at the end of the study when differences are computed, whereas the measurement error variance contributes only once to the total variance of cross-sectional data. The total variance for change data, however, is usually not twice as large as the total variance for the same variable measured cross-sectionally (e.g., see Table 1).

Change in total weight can be measured more precisely than changes in fat body mass, lean body mass, or regional adiposity (unpublished results). We estimate that the addition of measurement error may underestimate the correlations of Table 2 by about 6% for total weight change, about 17% for fat body mass change, 48% for lean body mass change, and 56% for changes in the ratio of waist-to-hip girth. In contrast, the measurement error bias is expected to underestimate cross-sectional correlations at baseline in these men by only 0.2% for total weight, 3% for fat body mass, 1.6% for lean body mass, and 4% for the ratio of waist to hip girth. These calculations show that a greater bias due to measurement error is expected when Δ lipoproteins are correlated with Δ waist-to-hip girth and Δ lean body mass, than with Δ total body mass and Δ fat body mass. From these results, we conclude that lipoprotein concentrations may correlate more strongly with the ratio of waist girth to hip girth than other adiposity measures for cross-sectional comparisons, but not for change data because of the greater contribution of measurement error variance when changes are computed. We also conclude that correlations involving changes in lean body mass may be insensitive to possible associations between increased muscle mass and lipoprotein concentrations because there is a large measurement error bias for lean body mass.
Effects of Running and Weight Loss on Coronary Heart Disease Risk

There is a close correspondence between the measurements of LDL peak flotation rate by analytic ultracentrifugation and the major peak of the LDL by gradient gel electrophoresis (Krauss RM, Burke DJ, unpublished observations). A high concentration of small LDL particles and a gradient gel electrophoretic LDL lipoprotein profile with a major peak less than or equal to 255 Å characterize a type B LDL phenotype, whereas a predominance of large LDL particles and a major peak greater than 255 Å characterizes a type A phenotype.39 Austin et al.30 have proposed that a dominant allele with a gene frequency of about 0.25 may predispose individuals to the type B phenotype pattern.39 Therefore, the decrease in small LDL concentrations and the increase in LDL peak flotation rate due to exercise or weight loss represents a shift from the type B phenotype toward the type A phenotype. Austin et al. report that there is a two- to threefold increased risk of myocardial infarction in persons with type B phenotype compared with type A phenotype.40 The results presented in this report and in our previous cross-sectional study1 suggest that long distance running and weight loss may reduce coronary heart disease risk in persons genetically predisposed to this high-risk lipoprotein profile.

Appendix

Reproducibility of Lipoprotein Subfraction Measurements by Analytic Ultracentrifugation

Repeated lipoprotein measurements taken in the same person on different days will vary because of metabolic changes that occur within individuals (i.e., within-person sampling error) and because of variations in sampling protocol, laboratory conditions, and instrument performance (measurement error). Both sources of error dilute the associations between usual lipoprotein concentrations and other variables.38 To assess the reproducibility of lipoprotein subfraction measurements over time, lipoprotein mass concentrations from two serum samples drawn (mean ± SD) 19.3±9.7 days apart were obtained in 26 men. The Appendix table shows that the mean lipoprotein changes between the two visits were modest and not significantly different from 0. Correlations near 1 indicate relatively little measurement error, and correlations near 0 may indicate substantial measurement error relative to the total variation. The within-person component of variance was estimated by the standard deviation for the difference between the two measurements.

The correlations suggest that measurements of HDL2 mass and HDL3 mass concentrations were only slightly less reproducible over time than HDL cholesterol (r=0.82). Analytic ultracentrifuge measurements of small LDL and total VLDL mass concentrations and LDL peak flotation rate were as reproducible over time as LDL+IDL cholesterol (r=0.82). The analytic ultracentrifuge appears to be able to measure total VLDL mass concentrations with greater consistency in individuals over time than the direct measurement of VLDL cholesterol by Lipid Research Clinics procedures (r=0.58). The 95% confidence interval shows that our data do not provide a very precise estimate of the reproducibility of the large VLDL measurements.

The two HDL subfractions had similar correlations for repeated measurements. Therefore, the significant correlations of both exercise and weight loss with HDL2 and not HDL37,8 are not likely to be due to greater precision in the HDL2 measurement than in the HDL3 measurement. Adiposity may correlate less strongly with IDL than with small LDL and total VLDL (Table 2) in part because the IDL measurements are less reproducible.

The Appendix figure displays the correlations between repeated lipoprotein mass measurements for individual flotation intervals of HDL, LDL, and IDL. Lipoprotein mass measurements of the least dense and most dense HDL particles are relatively unstable, as are mass measurements of S0 to 2 and S10 to 12 within the LDL and IDL distribution. This figure suggests that, in some cases, significant associations may be observed for specific regions of the lipoprotein distribution because some flotation intervals are more precisely measured. For example, weight loss correlates significantly with lipoprotein mass changes within S0 to 2 and not within S0 to 2 (see
Appendix figure. Pearson correlations between repeated lipoprotein mass measurements for individual flotation intervals of high density lipoproteins (HDL), low density lipoproteins (LDL), and intermediate density lipoproteins (IDL) from two serum samples drawn (mean±SD) 19.3±9.7 days apart in a subset of 26 men at baseline. Correlations near 1 indicate relatively little measurement error, and correlations near 0 may indicate substantial measurement error relative to the total variation.

Results, and adipose tissue lipoprotein lipase activity correlates significantly with $S_r$ 2 to 4 and not within $S_r$ 0 to 2. These results may have been observed because concentrations of $S_r$ 0 to 1 and $S_r$ 1 to 2 were measured less precisely. The low precision of the $S_r$ 0 to 2 measurement is probably due to the limited sensitivity of the instrument at low mass concentrations but may also partly reflect the accumulated error from several components that may occur within this particle flotation range and that may vary over time; these components include the small LDL particles, HDL, and Lp(a).$^{42}$

The figure also shows that repeated lipoprotein mass measurements of $S_r$ 10 to 12 for LDL and IDL correlate less strongly than lipoprotein mass measurements of adjacent intervals. The low correlation may designate an overlapping region where the tails of the LDL and the IDL distributions overlap. Therefore, this interval may reflect the combined variability (i.e., the accumulated measurement error) of both components. The tails of the two particle distributions may be less stable than the central part of either distribution. Gofman$^{43}$ originally separated LDL from IDL at $S_r$ 10, but later defined IDL as $S_r$ 12 to 20, corresponding to $1.006 \leq \text{density} \leq 1.019$, to minimize the overlap of IDL with LDL.$^{44}$ However, smaller cholesterol-enriched IDL species have been shown to have buoyant densities up to $1.030 \text{g/ml}$ and corresponding peak $S_r$ rates of $S_r$ 10 to 16.$^{45}$ Our results suggest that the $S_r$ 10 to 12 flotation interval may be appropriately combined with either LDL or IDL.

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