Caloric Restriction with or without Exercise: The Fitness versus Fatness Debate

D. ENETTE LARSON-MEYER1,2, LEANNE REDMAN1, LEONIE K. HEILBRONN3, CORBY K. MARTIN1, and ERIC RAVUSSIN1

1Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA; 2University of Wyoming, Laramie, WY; and 3Garvan Institute, Sydney, AUSTRALIA

ABSTRACT

LARSON-MEYER, D. E., L. REDMAN, L. K. HEILBRONN, C. K. MARTIN, and E. RAVUSSIN. Caloric Restriction with or without Exercise: The Fitness versus Fatness Debate. Med. Sci. Sports Exerc., Vol. 42, No. 1, pp. 152–159, 2010. There is a debate over the independent effects of aerobic fitness and body fatness on mortality and disease risks. Purpose: To determine whether a 25% energy deficit that produces equal change in body fatness leads to greater cardiometabolic benefits when aerobic exercise is included. Methods: Thirty-six overweight participants (16 males/20 females) (39 ± 1 yr; 82 ± 2 kg; body mass index = 27.8 ± 0.3 kg/m², mean ± SEM) were randomized to one of three groups (n = 12 for each) for a 6-month intervention: control (CO, weight-maintenance diet), caloric restriction (CR, 25% reduction in energy intake), or caloric restriction plus aerobic exercise (CR + EX, 12.5% reduction in energy intake plus 12.5% increase in exercise energy expenditure). Food was provided during weeks 1–12 and 22–24. Changes in fat mass, visceral fat, V˙O₂peak (graded treadmill test), muscular strength (isokinetic knee extension/flexion), blood lipids, blood pressure, and insulin sensitivity/secretion were compared. Results: As expected, V˙O₂peak was significantly improved after 6 months of intervention in CR + EX only (22 ± 5% vs 7 ± 5% in CR and −5 ± 3% in CO), whereas isokinetic muscular strength did not change. There was no difference in the losses of weight, fat mass, or visceral fat and changes in systolic blood pressure (BP) between the intervention groups. However, only CR + EX had a significant decrease in diastolic BP (−5 ± 3% vs −2 ± 2% in CR and −1 ± 2% in CO), in low-density lipoprotein (LDL) cholesterol (−13 ± 4% vs −6 ± 3% in CR and 2 ± 4% in CO), and a significant increase in insulin sensitivity (66 ± 22% vs 40 ± 20% in CR and 1 ± 11% in CO). Conclusions: Despite similar effect on fat losses, combining CR with exercise increased aerobic fitness in parallel with improved insulin sensitivity, LDL cholesterol, and diastolic BP. The results lend support for inclusion of an exercise component in weight loss programs to improve metabolic fitness. Key Words: EXERCISE TRAINING, MAXIMAL AEROBIC FITNESS, ENERGY RESTRICTION, BLOOD PRESSURE, BLOOD LIPIDS

Numerous studies have linked increased adiposity (17,32) and reduced physical activity (17) and/or fitness (32,35) to increased risk of cardiovascular disease (CVD) and overall mortality. However, because of the strong link between physical fitness—particularly of aerobic nature—and reduced prevalence of obesity (35,38), there is debate about the potential independent effects of aerobic fitness and adiposity (i.e., fatness) on CVD and metabolic health risk factors. For example, it is generally recognized that the benefits of increased physical activity on CVD risks include decreased platelet aggregation, enhanced fibrinolysis, decreased susceptibility to malignant ventricular arrhythmias, improved endothelial function, and myocardial oxygen delivery, along with reduced obesity (12). The detriments of increased fatness, on the other hand, include increased renin-angiotensin system activation (10), low-grade inflammation (2,39), and chronic oxidative stress (20) which result in reduced nitric oxide availability, increased vascular tone and arterial stiffening, and increased systolic and pulse pressures (8,29). Furthermore, both fatness and poor fitness are linked with insulin resistance, elevated blood pressure, and elevated total and low-density lipoprotein (LDL) cholesterol concentrations (12), all of which improve with weight loss and enhanced fitness. These links are of course complicated by the strong negative relation between fitness and fatness.

Although several large studies (18) including the Nurses Health Study (17) and the Lipid Research Clinic Study (32)
have provided evidence supporting independent contributions of both decreased physical activity/fitness and increased fatness on mortality, there are several reports predominately from Blair’s group (4,5,23,33,34) suggesting that aerobic fitness can negate the adverse effects of fatness on mortality (4,33,34). Such results have often been interpreted that reducing fatness is not necessary in light of adequate fitness (24). The majority of previous studies, however, have been criticized for inclusion of mostly relatively young healthy white individuals rather than a more ethnically representative sample of aging individuals (38). In contrast, analysis from the Look AHEAD (Action for Health in Diabetes) Trial in a large ethnically diverse sample of overweight individuals with type 2 diabetes found that both fitness and fatness are related to CVD risk factors, but that the strength of the association for fitness versus fatness was different for different risk factors (38). These results along with a few other trials (3,19) suggest that both fitness and reduced fatness are important for reducing overall morbidity and mortality.

An interesting question still up for debate is whether improvements in fitness or fatness independently alter risk factors for CVD and the metabolic syndrome, particularly during caloric restriction (CR). Prolonged CR increases life span in rodents and other shorter-lived animal species (36), but the addition of exercise improves average life span but not maximal life span (16). In humans, CR has been shown to impact several biomarkers of longevity including fasting insulin concentration, body core temperature (14), DNA damage (14), and markers of atherosclerosis (9). It is, however, not known if in a prospective design, the addition of exercise training will yield extra health benefit in the face of similar weight and fat loss. In other words, does CR with or without exercise result in different improvements in cardiometabolic risk factors which could ultimately improve longevity? The purpose of this analysis was to determine whether a deficit by energy restriction or energy restriction plus aerobic exercise that produces equal change in fatness (26) leads to greater cardiometabolic benefits when exercise is included.

**RESEARCH METHODS AND PROCEDURES**

This evaluation was performed as part of a randomized clinical trial designed to examine the effects of CR on markers of longevity in nonobese humans referred to as the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy study (CALERIE; Trial registration: ClinicalTrials.gov Identifier: NCT00099151). Details of the study have been published elsewhere (14). Briefly, we enrolled overweight men and women (25≤ screening, body mass index (BMI) < 30 kg·m⁻²) aged 25–45 yr for women and 25–50 yr for men with no personal history of type 2 diabetes, CVD, high blood pressure (>160/90 mm Hg), liver disease, obesity, psychiatric or eating disorders, alcoholism or substance abuse, and not taking any medical treatment. The study was approved by our Institutional Review Board, and all participants gave written informed consent before participation.

**Intervention.** After a 5-wk baseline assessment, 36 participants were randomized into one of three groups (n = 12 for each): 25% caloric restriction (CR) from baseline energy requirements; 12.5% CR + 12.5% increase in total energy expenditure through structured exercise (CR + EX); and control (CO) with weight-maintenance by a healthy diet (American Heart Association Step 1 diet). An additional 12 subjects were also randomized into a low-caloric diet rapid weight loss group (15%), but this group is not included in the current analysis because the participants did not exercise and lost a greater amount of body weight. Subjects were stratified according to sex, race, and screening BMI before sequential randomization. Baseline energy requirements were determined from individual free-living energy expenditure assessed over 4 wk using doubly labeled water (14).

**Diets.** All diets were based on the American Heart Association Step 1 recommendations (<30% fat; ≤10% saturated fat) and provided the recommended daily allowance for all essential vitamins and minerals. For the first 12 wk after randomization, the diet for all groups was provided by our metabolic kitchen (14). During weeks 13–22, participants self-selected their own diet based on their individual caloric target, before returning to the in-feeding protocol for weeks 22–24.

**Structured exercise.** Except for the CR + EX group, other participants were not permitted to modify their physical activity patterns. The CR + EX group was required to increase energy expenditure by 12.5% above baseline requirements by undergoing structured aerobic exercise (i.e., walking, running, or stationary cycling) 5 d·wk⁻¹ according to an individualized exercise prescription. The target energy cost of the exercise sessions was calculated from the weekly desired energy cost divided by 5 d·wk⁻¹. Five rather than 7 d·wk⁻¹ of exercise was selected to comply with the American College of Sports Medicine recommendations of 3–5 d·wk⁻¹ of aerobic exercise (1). Individual exercise prescriptions to meet target goals were calculated by measuring the oxygen cost (V-Max 29 Series; SensorMedics, Yorba Linda, CA) during three individually prescribed levels of activity (i.e., walking at 3.0, 3.5, and 4.0 mph), generating an energy cost equation from the workload versus oxygen cost above rest (i.e., net oxygen consumption), and assigning exercise duration according to target energy expenditure and self-selected workload. Energy equivalents were determined using the calculated food quotient of 4.89 kcal·L⁻¹ of oxygen consumed.

To prevent skeletal muscle soreness and injury, the exercise load was progressively increased during the initial 6 wk, whereas energy intake was adjusted so that the energy deficit always equaled 25% of the daily energy requirements. After week 6, participants were allowed to select their exercise intensity (as long as their heart rate was within 65%–90% of maximal heart rate [1]), and exercise...
duration was adjusted to maintain the target energy expenditure. During the first 6 wk, all exercise sessions were conducted at the Pennington Biomedical Research Center (PBRC) Health and Fitness Center under supervision. For weeks 7–24, at least three of the five weekly sessions were conducted at the center under supervision. A wireless heart rate monitor (Polar S-610; Polar Beat, Port Washington, NY) was used to record exercise duration and average heart rate during both supervised and unsupervised sessions. The average energy cost throughout the intervention was 403 ± 63 kcal per session for women and 569 ± 118 kcal per session for men which resulted in an average exercise duration of 53 ± 11 min and 45 ± 14 min per session for women and men, respectively.

Behavior and compliance strategies. Cognitive-behavioral techniques were used to foster adherence to diet and exercise prescription, including self-monitoring and stimulus control (14). All participants attended weekly group meetings and were contacted once per week via telephone to address any adherence problems quickly. Both direct observation and heart rate data (from both supervised and unsupervised sessions) were used to assess exercise compliance.

Metabolic testing. Subjects were tested during a 5-d admission to the clinical research center at baseline (week 0) and week 24 (14) (Fig. 1). Testing included dual energy x-ray absorptiometry to assess total body composition (Hologic QDR 4500A, QDR for Windows Version 11.1.2; Hologics, Bedford, MA); multislice computed tomography scanning of the abdominal region to assess total, visceral, and subcutaneous abdominal adipose tissue (31); and a frequently sampled intravenous glucose tolerance test (28,37) to assess insulin sensitivity. More specifically, abdominal fat was measured on a GE LightSpeed Plus CT scanner (General Electric Medical Systems, Milwaukee, WI). Eight contiguous images (1-cm slice thickness) were acquired every 5 cm—5 above and 2 below a slice centered on the lumbar 4–lumbar 5 intervertebral disc using 170 mA, a scan time of 1 s, and a 512 × 512 matrix. Total, visceral, and subcutaneous abdominal fat were defined using Analyze 3.0 (Biomedical Imaging Resource, Mayo Clinic, Rochester, MN) by selecting regions of interest as previously described in detail (31). Briefly, total abdominal fat was defined as the sum of adipose tissue pixels (~30 to ~190 Hounsfield units) inside a line tracing the skin, whereas visceral abdominal fat was segmented by drawing a line around the interior of the peritoneal cavity and summing all adipose tissue pixels within the area. Subcutaneous abdominal fat was calculated as the difference between total abdominal fat and visceral abdominal fat. Measurements of systolic and diastolic blood pressure were taken twice, 5 min apart, in a quite room at thermoneutrality from the participant’s right arm with a manual sphygmomanometer by a certified staff member after 10 min of seated rest. A fasting blood sample was also drawn for determination of serum lipids. Several days before the inpatient admission, aerobic fitness was assessed by a progressive treadmill test to exhaustion (VO_{2peak} test), and isokinetic muscle “strength” and endurance of the quadriceps

FIGURE 1—Overview of CALERIE study.

TABLE 1. Baseline demographic and metabolic characteristics of subjects by treatment group.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>CR</th>
<th>CR + EX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>5/6</td>
<td>5/6</td>
<td>5/7</td>
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<tr>
<td>Age (yr)</td>
<td>38 ± 8</td>
<td>39 ± 5</td>
<td>36 ± 6</td>
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<tr>
<td>Body mass (kg)</td>
<td>81.8 ± 9.3</td>
<td>80.9 ± 11.4</td>
<td>81.9 ± 10.5</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>27.6 ± 2.0</td>
<td>27.8 ± 1.4</td>
<td>27.5 ± 1.6</td>
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<td>Body fat (%)</td>
<td>32.2 ± 6.6</td>
<td>30.9 ± 8.3</td>
<td>32.6 ± 2.2</td>
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<tr>
<td>Metabolic profile</td>
<td></td>
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<tr>
<td>Total cholesterol (mg,\text{dL}^{-1})</td>
<td>175 ± 33</td>
<td>177 ± 25</td>
<td>169 ± 33</td>
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<tr>
<td>HDL cholesterol (mg,\text{dL}^{-1})</td>
<td>38 ± 15</td>
<td>41 ± 9</td>
<td>44 ± 8</td>
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<tr>
<td>LDL cholesterol (mg,\text{dL}^{-1})</td>
<td>110 ± 32</td>
<td>107 ± 24</td>
<td>105 ± 28</td>
</tr>
<tr>
<td>Triglycerides (mg,\text{dL}^{-1})</td>
<td>134 ± 65</td>
<td>146 ± 113</td>
<td>98 ± 66</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>113 ± 12</td>
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<td>111 ± 10</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>74 ± 10</td>
<td>72 ± 8</td>
<td>72 ± 8</td>
</tr>
<tr>
<td>Insulin sensitivity (U,\text{mL}^{-1})</td>
<td>2.8 ± 1.2</td>
<td>3.3 ± 1.7</td>
<td>3.4 ± 0.4</td>
</tr>
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</table>
was measured using a Cybex II Isokinetic Dynamometer, (Cybex Division of Lumex, Inc, Ronkonkoma, NY).

**Aerobic fitness.** Maximal oxygen uptake (VO₂peak) was performed in the morning after an overnight fast by a progressive treadmill test to exhaustion (1). Following a 6-min warm-up, subjects began walking or running (depending on their fitness level) at a pace that elicited a heart rate of between 120 and 140 bpm, after which the workload was progressively increased by 2% in grade every min until volitional fatigue. O₂ consumption (VO₂) and CO₂ production (VCO₂) were measured continuously using a metabolic cart (V-Max 29 Series; SensorMedics) that was calibrated before each test. Heart rate was monitored continuously using a portable heart rate monitor (Polar S-610; Polar Beat). The highest VO₂, RER, and heart rate achieved over a 20-s period within the last 2 min of exercise were recorded as the maximum values.

**Muscle strength.** Isokinetic strength and endurance were measured using a Cybex II Isokinetic Dynamometer (Cybex Division of Lumex, Inc) during knee extension and flexion. The procedure involved an initial test of three repetitions at 60° s⁻¹ to measure peak force and power followed by a test to fatigue at 180° s⁻¹. Before testing, subjects underwent a familiarization trial.

**Serum lipids.** Total cholesterol, HDL cholesterol, and triglycerides were analyzed according to standardized procedures (25), and LDL cholesterol was calculated using the Friedwald equation.

**Statistical analysis.** Data are expressed as means ± SD, and the level of significance for all statistical tests was set at P < 0.05. SAS Version 9.1 was used for analysis, and all analyses were performed by a biostatistician. The change and percent change from baseline to month 3 and month 6 were computed for all variables, and ANOVA of the changes was used to determine differences. The factors tested in the model were treatment (CR, CR + EX, control), time (month 3, month 6), sex, and their interactions. Baseline values were included in the models as covariates. The statistical significance for all multiple comparisons was adjusted with respect to the Tukey–Kramer method to control for type I errors. One participant in the control group withdrew during the study (before month 3) for personal reasons. Data are therefore presented for 35 subjects.

**RESULTS**

**Baseline characteristics.** The characteristics of the 35 subjects and their cardiometabolic parameters at baseline have been previously published (14,22,25,26) but are described in Table 1. As expected, there was no difference among treatment groups at baseline.

**Effect of CR on body weight and body composition.** Details on the change in body weight and body composition have been previously reported (14,22,26). Briefly, and as summarized in Figures 2 and 3, body weight was significantly reduced from baseline (P < 0.001) by ~10% in both the CR and CR + EX groups at the end of

**FIGURE 2**—Change in body mass over the 6 months of treatment with control, caloric restriction (CR), and caloric restriction structured aerobic exercise (CR + EX). There were no significant differences between CR and CR + EX treatments. *Significant (P < 0.005) change from baseline.

**FIGURE 3**—Change in whole body fat mass and visceral fat stores after 6 months of treatment with control, caloric restriction (CR), and caloric restriction and structured aerobic exercise (CR + EX). There were no significant differences between CR and CR + EX treatments. *Significant (P < 0.005) change from baseline.
the 6-month intervention (Fig. 2). Total body fat mass and visceral abdominal fat were significantly \((P < 0.005)\) but similarly reduced in both intervention groups (by \(\sim 25\%\)) and unchanged in controls (Fig. 3).

**Effect of CR on aerobic fitness and isokinetic strength.** The change in maximal aerobic fitness (\(\dot{V}O_2\text{peak}\)) and isokinetic strength in the control, CR and CR + EX groups are summarized in Table 2. Absolute \(\dot{V}O_2\text{peak} (\text{L.min}^{-1})\) was significantly increased versus baseline by \(10 \pm 4\% (P < 0.01)\) in the CR+EX group and slightly but insignificantly \((P = 0.36)\) decreased by \(-4 \pm 5\%\) and \(-6 \pm 3\%\) in the CR and control groups, respectively. When adjusted for body weight, \(\dot{V}O_2\text{peak}\) was significantly improved by \(22 \pm 5\%\) in the CR + EX group \((P < 0.0001)\), slightly but nonsignificantly increased \((7 \pm 5\%; P = 0.06)\) in CR (mainly as a function of body mass reduction) and slightly but not significantly decreased in the control group \((-5 \pm 3\%; P > 0.20)\). Findings were similar when expressed as METs. In the CR + EX group, METs increased by \(18 \pm 6\% (P < 0.001)\) but the change in METs was not significant from baseline in the CR group \((7 \pm 6\%)\) or control \((-2 \pm 5\%)\). There were no changes in peak torque or average power during isokinetic quadriceps flexion or extension.

**CR and cardiometabolic risk factors.** The change in systolic blood pressure, diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and insulin sensitivity have been previously reported (14,22,25) and are

| TABLE 2. The change in maximal aerobic fitness (\(\dot{V}O_2\text{peak}\)) isokinetic strength in the control, CR, and CR + EX. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Control         | CR              | CR + EX         | Control         | CR              | CR + EX         |
|                  | Baseline        | 6 Months        | Baseline        | 6 Months        | Baseline        | 6 Months        |
| Aerobic fitness |                 |                 |                 |                 |                 |                 |
| \(\dot{V}O_2\text{peak} (L)\) | 2.56 ± 0.18     | 2.43 ± 0.20     | 2.61 ± 0.25     | 2.47 ± 0.26     | 2.54 ± 0.20     | 2.76 ± 0.21*    |
| \(\dot{V}O_2\text{peak} (mL.kg}\text{^{-1}.min}^{-1}\) | 30.9 ± 1.6      | 29.5 ± 1.8      | 31.1 ± 2.1      | 33.5 ± 3.0      | 30.6 ± 1.5      | 37.0 ± 1.7*     |
| \(\dot{V}O_2\text{peak} (METs)\) | 8.7 ± 0.5       | 8.5 ± 0.5       | 9.0 ± 0.6       | 9.7 ± 0.8       | 8.7 ± 0.4       | 10.3 ± 0.6*     |
| Isokinetic strength |                 |                 |                 |                 |                 |                 |
| Peak torque, extension (ft/lb) | 115.2 ± 9.5     | 106.6 ± 9.5     | 112.0 ± 12.1    | 112.2 ± 12.0    | 105.5 ± 10.7    | 95.6 ± 9.2      |
| Peak torque, flexion (ft/lb) | 65.4 ± 7.0      | 69.6 ± 8.0      | 67.2 ± 10.7     | 74.2 ± 8.3      | 66.9 ± 10.4     | 68.2 ± 9.0      |
| Average power extension, 180 rpm | 138.8 ± 16.5    | 168.3 ± 17.7    | 156.8 ± 22.3    | 172.7 ± 24.4    | 138.8 ± 22.4    | 168.3 ± 17.1    |
| Average power extension, 60 rpm | 101.4 ± 9.2     | 92.9 ± 8.2      | 98.0 ± 11.9     | 101.6 ± 11.2    | 88.6 ± 11.7     | 82.8 ± 8.3      |
| Average power flexion, 180 rpm | 121.2 ± 13.7    | 129.8 ± 13.3    | 121.2 ± 19.0    | 124.9 ± 20.4    | 104.5 ± 19.1    | 125.8 ± 17.6    |
| Average power flexion, 60 rpm | 67.8 ± 8.9      | 68.0 ± 7.8      | 66.4 ± 10.8     | 73.7 ± 8.8      | 62.6 ± 9.6      | 62.5 ± 8.5      |

* Significant difference versus baseline \((P < 0.05)\).

FIGURE 4—Change in cardiometabolic risk factors after 6 months of treatment with control, caloric restriction (CR), and caloric restriction and increased structured exercise (CR + EX). Diastolic blood pressure, total cholesterol, LDL cholesterol, HDL cholesterol, and insulin sensitivity were significantly improved versus baseline in the CR + EX group but not in the CR or control groups. Systolic blood pressure was not changed by any of the treatments groups, whereas HDL was significantly \((P < 0.05)\) increased in all treatment groups (including the control). *Significant \((P < 0.05)\) change from baseline.
summarized in Figure 4. Although HDL was significantly ($P < 0.05$) increased in all treatment groups (including the control), diastolic blood pressure, total cholesterol, LDL cholesterol, and insulin sensitivity were significantly ($P < 0.02$) improved versus baseline only in the CR + EX group but not in the CR or control groups. Systolic blood pressure was not changed by any of the treatments. Fasting serum triglyceride concentration (not shown) increased significantly ($P < 0.05$) by $28 \pm 11\%$ in the control group but decreased $-21 \pm 5\%$ and $-15 \pm 6\%$, respectively, in both CR and CR + EX groups ($P < 0.001$ vs baseline and control).

**DISCUSSION**

In this randomized clinical trial, we tested the effect of body weight and body fat loss with or without improvement in physical fitness on cardiometabolic risk factors in overweight men and women who underwent a 6-month CR regimen with or without regular aerobic exercise. Although both intervention groups experienced similar reductions in total body mass, fat mass, and visceral abdominal mass, the caloric restricted plus exercise group experienced greater improvement in insulin sensitivity, LDL cholesterol, and diastolic blood pressure than that in the CR by diet alone group. Our results strongly suggest that inclusion of regular aerobic exercise (or training) in a weight loss program yields cardiometabolic health benefits beyond those of weight loss alone. Our results further support the argument that both fitness and fatness are important for reducing cardiometabolic risks, particularly during CR and may shed some light on how fitness or fatness may contribute to overall mortality.

The main difference between the two caloric-restricted groups was that one group was 25% caloric restricted by diet alone (i.e., consuming 75% of requirement), whereas the other group was in 25% energy deficit, 12.5% by decreasing food intake, and 12.5% by increasing energy expended through regular aerobic exercise. Not surprisingly, the caloric restricted plus exercise group experienced significant improvements in aerobic fitness with an average 10% improvement in absolute $\dot{V}O_{2peak}$ (L·min$^{-1}$) and an average 22% improvement in $\dot{V}O_{2peak}$ relative to body weight. Of interest, however, is the slight albeit not statistically significant decrease in absolute aerobic fitness that occurred over the 6-month period in both the non-exercise groups. In comparison, Ross et al. (27) found that weight loss induced by a 700-kcal daily energy deficit by diet resulted in a 5% decrease in aerobic fitness, whereas weight loss induced by a 700-kcal increase in exercise resulted in a 13% improvement in $\dot{V}O_{2peak}$. In the current study, however, CR either by diet or diet plus exercise did not result in any significant changes in leg muscle peak power or endurance. Importantly, our data demonstrate that CR does not lead to reduced overall strength or functionality in humans when fed a nutritionally sound diet.

A unique aspect and strength of the study is that weight loss was achieved through provision of isoenergetic deficits (regardless of exercise) which resulted in almost identical reductions in total body weight and total and visceral adiposity (26). Such design allows us to tease out the additional influence of exercise which according to our results is a necessary part of the prescription to gain full cardiometabolic improvements including improved insulin sensitivity and lowered LDL cholesterol and diastolic blood pressure. The statistically significant improvement in insulin sensitivity only in the CR + EX, but not CR group, is not surprising given the well-documented insulin-sensitizing effect of aerobic exercise (15) driven predominantly by increased glucose transporter 4 (GLUT4) expression and trafficking in exercised skeletal muscle (11). Increased fatness, on the other hand, is associated with increased ectopic fat deposition in skeletal muscle and liver (22) which may influence the insulin signaling cascade (30) and impact circulating lipids (30). Somewhat surprising, however, is that inclusion of aerobic exercise did not result in additional improvements in HDL cholesterol (21) and to a lesser extent systolic blood pressure (13). Such lack of effect may be related to our selection of healthy overweight rather than obese volunteers (who had relatively normal blood pressure values) and our administration of a tightly controlled AHA-Step 1 diet which provided 30% of energy from fat.

The results of the current study along with those of a previous analysis reporting larger reduction in 10-yr CVD risk (38% in CR + EX vs 29% in CR and no change in controls) (25) when exercise was included suggest that improvements in both fitness and fatness are needed for optimally reducing overall morbidity and mortality. Results are in agreement with cross-sectional analysis of the Look AHEAD study in which fitness and fatness had different impacts on CVD risk factors, although these two variables are clearly strongly related (38). Specifically, aerobic fitness (assessed by $\dot{V}O_{2peak}$) had stronger associations than fatness with the Framingham Risk Score (model used to identify healthy individuals at risk for CVD), the ankle/brachial index (average ankle systolic blood pressure/arm systolic blood pressure; a physiological marker of cardiovascular risk), and hemoglobin A1C concentration (a marker of diabetes control). Our results further suggest that regular aerobic exercise which improves $\dot{V}O_{2peak}$ also improves peripheral resistance during diastole above that noted with a reduction in fatness (25). Although it is clearly established that elevated systolic blood pressure is a more powerful predictor of cardiovascular events than diastolic pressure (6,7), increased diastolic blood pressure causes an increased risk for end organ failure (7), cardiovascular death (6), and could indeed be an important reason why fitness is associated with reduced overall mortality.

Another important health benefit exerted by regular exercise beyond those of weight loss includes its impact on aerobic capacity, particularly in relation to daily functionality and overall mortality. Aerobic capacity has
been shown to be a more powerful predictor of mortality among both healthy men and those with CVD than other established risk factors with each 1-MET increase in aerobic capacity conferring a 12% increase in survival. Based on these reported statistics, our CR + EX group, who improved their aerobic capacity by an average 1.6 METs would have an estimated 19.2% increase in survival. By contrast, the improvement in the aerobic capacity of the CR + EX group was parallel with an alarming tendency of absolute aerobic capacity to decline over the 6-month period in both the CR and control-treated groups.

Although this randomized clinical trial is in support of the argument that exercise training offers benefits beyond improved fatness, it was conducted in a small sample (relative to epidemiological trials) of 35 healthy overweight volunteers with limited health risk factors and without groups such as exercise alone (25% energy deficit via exercise energy expenditure) or exercise without weight loss (12.5% increase in energy expenditure with 12.5% increase in energy intake). Such groups would have helped to distinguish between the metabolic effects of fitness compared with fatness alone. Both groups, however, would have been almost impossible: for example, participants in the CR plus structured exercise group exercised an average of 45–53 min at least 5 d wk\(^{-1}\) to achieve the 12.5% of energy expenditure which would have had to be doubled to promote 25% energy expenditure. Unfortunately, our relatively small sample size of mostly healthy overweight volunteers also limited our power to detect differences among treatments for improvements in cardiometabolic risk factors (22). These limitations, however, were compensated in part by the very tight control of the intervention and control groups including the rigorously controlled diet and structured exercise program.

Results of the current study suggest that beyond changes in fatness, combining CR with exercise is important for increasing aerobic fitness and optimizing improvements in risk factors for diabetes and CVD, including improved insulin sensitivity, LDL cholesterol, and diastolic blood pressure that are beyond those of body weight/body fat reduction alone. Improvements in other cardiometabolic risk factors, however, such as systolic blood pressure and HDL cholesterol might only be associated with changes in fatness and/or consumption of a healthy diet.

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