Effects of matched weight loss from calorie restriction, exercise, or both on cardiovascular disease risk factors: a randomized intervention trial[1]

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ABSTRACT

Background: Weight loss from calorie restriction (CR) and/or endurance exercise training (EX) is cardioprotective. However CR and EX also have weight loss–independent benefits.

Objective: We tested the hypothesis that weight loss from calorie restriction and exercise combined (CREX) improves cardiovascular disease (CVD) risk factors more so than similar weight loss from CR or EX alone.

Design: Overweight, sedentary men and women ($n = 52$; aged 45–65 y) were randomly assigned to undergo 6–8% weight loss by using CR, EX, or CREX. Outcomes were measured before and after weight loss and included maximal oxygen consumption (VO_{2max}), resting blood pressure, fasting plasma lipids, glucose, C-reactive protein, and arterial stiffness [carotid–femoral pulse wave velocity (PWV) and carotid augmentation index (AI)]. Values are means ± SEs.

Results: Reductions in body weight ($\sim 7\%$) were similar in all groups. VO_{2max} changed in proportion to the amount of exercise performed (CR, $-1\% \pm 3\%$; EX, $+22\% \pm 3\%$; and CREX, $+11\% \pm 3\%$). None of the changes in CVD risk factors differed between groups. For all groups combined, decreases were observed for systolic and diastolic blood pressure (-5 ± 1 and -4 ± 1 mm Hg, respectively; both $P < 0.0008$), total cholesterol (-17 ± 4 mg/dL; $P < 0.0001$), non-HDL cholesterol (-16 ± 3 mg/dL; $P < 0.0001$), triglycerides (-18 ± 8 mg/dL; $P = 0.03$), and glucose (-3 ± 1 mg/dL; $P = 0.0003$). No changes were observed for HDL cholesterol ($P = 0.30$), C-reactive protein ($P = 0.10$), PWV ($P = 0.30$), or AI ($P = 0.84$). These changes would be expected to decrease the lifetime risk of CVD from 46% to 36%.

Conclusion: Matched weight losses from CR, EX, and CREX have substantial beneficial effects on CVD risk factors. However, the effects are not additive when weight loss is matched. This trial was registered at clinicaltrials.gov as NCT00777621. *Am J Clin Nutr* 2016;104:576–86.

Keywords: weight management, overweight and obesity, adiposity, diet modification, aerobic exercise, cardiovascular disease, coronary heart disease, atherosclerosis

INTRODUCTION

Cardiovascular disease (CVD)[6] is the leading cause of death in the United States, accounting for 35% of adult deaths (1).

Observational studies indicate that excess body weight and adiposity are associated with an increased CVD risk (2). Furthermore, intervention studies show that weight loss has beneficial effects on CVD risk factors (3, 4), and would therefore be expected to prevent CVD. Dietary calorie restriction (CR) and endurance exercise training (EX) both can cause energy deficits and weight loss (5, 6), and consequently improve CVD risk factors (7). However, dietary changes and exercise also have effects on CVD risk factors through mechanisms that do not depend on weight loss. For example, in the absence of weight loss, the Dietary Approaches to Stop Hypertension diet reduces blood pressure (BP) (8), and a diet that is rich in plant sterols, soy protein, fiber, and nuts reduces serum LDL cholesterol concentrations (9). Furthermore, EX is associated with lower BP (10, 11), a better serum lipid profile (12), and lower CVD mortality (13) in a manner that does not appear to depend on body weight or weight loss.

We previously demonstrated that weight loss induced by CR alone and EX alone have similar beneficial effects on CVD risk factors (7). However, calorie restriction and exercise combined (CREX) was not studied. In light of the weight loss–independent effects of diet and exercise on CVD risk factors, it is conceivable that they may have additive effects. Therefore, the purpose of the present study (NCT00777621) was to test the hypothesis that modest weight loss in overweight men and women has greater beneficial effects on CVD risk factors when it is induced by

CREX than it does when similar weight loss is caused by CR or EX alone. The data reported in this manuscript were ancillary outcomes that were collected as part of a study on the effects of CR and exercise on glucose and insulin metabolism; the primary outcomes have been published previously (14) and therefore are not included in the present report. Some of the results related to intervention adherence were presented in the earlier paper and are provided again in the present report to assist with interpretation of the results.

METHODS

Participants

Sedentary, middle-aged men and postmenopausal women aged 45–65 y who were overweight [BMI (in kg/m^2) 25.0–29.9] were recruited from the Saint Louis, Missouri, metropolitan area. Screening tests, including a medical evaluation and diagnostic electrocardiogram exercise stress test were used to identify and exclude volunteers with major chronic diseases, conditions that would interfere with exercise or in which exercise is contra-indicated, or conditions that would interfere with interpretation of results. Examples include a history or evidence of coronary artery disease, musculoskeletal problems, diabetes (previously diagnosed or fasting blood glucose ≥126 mg/dL), BP of ≥160 mm Hg systolic or ≥100 mm Hg diastolic, and smoking. Use of medications to control blood glucose concentrations was exclusionary. For all other medications, participants were required to have been on stable dosages for ≥6 mo before baseline testing and were advised to maintain dosages during the study (none of the participants had changes in medications that affect serum lipids, BP, or heart rate (HR) during the study; 2 participants had changes in anti-inflammatory medications). Volunteers also were excluded if they had significant (>3%) weight change within the previous 6 mo and if they performed regular vigorous endurance exercise (moderate- to hard-effort exercise, ≥20 min/session, and ≥3 times/wk) during the 6 mo before enrollment.

Informed written consent to participate in the study was obtained from all volunteers who underwent screening. The study was approved by the institutional review boards at Saint Louis University and Washington University and was conducted from 2008 to 2015.

Study design and random assignment

Subjects were randomly assigned to the CR, EX, or CREX group. The randomization scheme included sex stratification and initially used a study group allocation ratio of 1:1:1. However, the ratio later was revised to 2:2:1 (greater enrollment in the CR and EX groups) to compensate for more subject withdrawals from these groups. Outcome assessments were performed at baseline and after weight loss.

Interventions

All 3 interventions were designed to create a 20% energy deficit and decrease body mass by 6–8% over 12–14 wk (i.e., a decrease of ∼0.5% of baseline body weight/wk). The intervention duration was extended as needed for individual participants to reach the weight loss goal. Prescriptions for dietary energy restriction and energy expenditure were based on estimates of baseline total energy expenditure (TEE) and energy intake, as follows: 1) Dietary Reference Intakes equations for estimated energy requirements (15), 2) 3-d food diaries with nutrient analysis (described below), 3) accelerometry (described below), and 4) 7-d physical activity recall interviews [(PARs) described below]. Because the participants were weight stable at baseline, which implied that TEE and energy intake were equal, the mean of all 4 measures was used to reflect TEE and energy intake. The prescriptions were adjusted as needed during the intervention to achieve the targeted rate of weight loss. Once the weight loss goal was attained, and to avoid the potentially confounding effects of a negative energy balance on the outcomes, body weight was stabilized for 2 wk (i.e., maintained within a 0.5-kg range based on 3-d rolling mean weight) by adjusting the CR and/or EX prescriptions. Throughout the study, the participants recorded daily fasting morning body weight at home and visited our clinic weekly to be weighed, turn in home weight logs, and undergo other intervention-specific requirements (described below).

CR intervention

The objective of the CR intervention was to reduce energy intake by ∼20% and maintain physical activity at baseline levels. The participants completed 3-d food diaries during the first 3 wk of the intervention and periodically thereafter; the study dietitians used the diaries as the basis for making personalized dietary recommendations. To reduce their energy intake, participants were advised to reduce food portion sizes and to replace energy-dense foods (e.g., cheeseburgers and soda) with foods of lower energy density (e.g., vegetables, fruits, and whole grains). Dietary advice also included recommendations for macronutrient intake to be within the recommended ranges (percentages of total energy: carbohydrate, 45–65; fat, 20–35; and protein, 10–35) (15). For participants who were not able to make adequate dietary changes on the basis of counseling alone, weeklong periods of full food provision (20% hypocaloric diet) were used as an additional intervention strategy.

EX intervention

The goal in the EX intervention was to increase TEE by ∼20% without dietary changes. Weekly exercise energy expenditure prescriptions were sufficient to increase total daily energy expenditure by 20%. The prescriptions were calculated after accounting for differences between gross and net exercise energy expenditure, as described previously (16). Participants monitored their progress toward the exercise energy expenditure goals with HR monitors (Polar) that provided estimates of exercise energy expenditure based on exercise HR, body weight, maximal oxygen consumption (VO$_{2max}$), and maximal and resting HR. The monitors stored exercise data (e.g., exercise energy expenditure, and HR, among others), which were retrieved by study personnel during weekly meetings with the participants. Specific prescriptions for exercise frequency and intensity were not provided. However, to increase the likelihood that they would meet the weekly energy expenditure goals, the participants were encouraged to perform exercise every day and to strive for moderate- and high-intensity exercise. The types of exercise that were recommended were cardiovascular

exercise (e.g., brisk walking and cycling) and functional physical activities (e.g., walking to work or performing yard work). Strength and resistance exercise was not used, because it only has a small effect on energy expenditure and may affect CVD risk through unique mechanisms. The participants exercised under the supervision of study personnel during the initial 3–6 exercise sessions and as needed thereafter to promote intervention compliance. Otherwise, the subjects were encouraged to exercise on their own (i.e., at a fitness facility, home, or outdoors), but were given free access to the on-campus exercise facilities.

CREX intervention

The CREX intervention was designed to create a 20% energy deficit by using a combination of CR and EX, with each contributing equally to the total deficit. The intervention methods were the same as those described for CR and EX.

Anthropometric measurements and body composition

Fasting morning body weight was measured on 2 separate days at each study time point. On each occasion, weight was measured in duplicate while the participant was wearing only a hospital gown and underwear. Standing height without shoes was measured with the use of a wall-mounted stadiometer. Circumferences were measured in duplicate and averaged; if the duplicates differed by ≥5 mm, additional measures were made until 2 values differed by <5 mm. Waist circumference was measured at the narrowest portion of the waist, inferior to the xiphoid and superior to the iliac crests. Hip circumference was measured at the maximal posterior protuberance of the buttocks. Dual-energy X-ray absorptiometry (Lunar iDXA, software version 13.31; GE Health care) was used to measure body composition. Body weight and composition data have been reported previously (14).

Dietary intake

Dietary intake was measured by using 3-d food diaries, each of which included 2 weekdays and 1 weekend day. The diaries were analyzed with Food Processor SQL software (ESHA Research). The assessments that were performed at the end of the intervention were performed just before the weight stability period to reflect the diet pattern that was used during active weight loss.

Energy expenditure

TEE was estimated as the mean of TEE results from PARs and accelerometry. The PAR was a modified version of the Stanford 7-d PAR (17). Accelerometry was performed with triaxial accelerometers (RT3; StayHealthy). Follow-up assessments were performed just before the weight stabilization period; therefore, the results reflect energy expenditure during active weight loss.

Aerobic capacity

VO_{2max} was determined by using indirect calorimetry (MedGraphics CardiO2; Medical Graphics Corporation) during a maximal graded exercise test to exhaustion with the use of a modified Balke protocol.

BP and resting HR

BP was measured by using a mercury sphygmomanometer and auscultation and was performed in accordance with American Heart Association guidelines (18), which also meet or exceed the recommendations of the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (19). At each time point in the study, morning fasting BP was measured on 2 separate days. The measures were made after ≥5 min of quiet rest with the arms supported and feet flat on the floor. Two measures were taken on each arm; if the results differed by ≥5 mm Hg, additional measures were made until the duplicates for each arm were within 5 mm Hg. The mean BP for both arms on both days were used as the study outcome.

Immediately after the BP measurement, HR was measured by palpating and counting the radial artery pulse for 60 s. The mean of measures made on 2 separate days was used as the study outcome.

Blood collection and analyses

After an overnight fast, blood was acquired from an arm vein; plasma and serum were isolated with the use of standard clinical methods. Plasma lipid concentrations were analyzed by a Clinical Laboratory Improvement Amendments-certified clinical laboratory at the medical center. C-reactive protein was measured in serum by using an ELISA (high sensitivity C-reactive protein, Quantikine; R&D Systems).

Fasting venous blood samples for quantification of glucose and insulin were acquired on 2 separate days and results were averaged. Plasma glucose was measured with the use of an automated analyzer based on the glucose oxidase reaction (2300 Stat Plus; YSI). Plasma insulin was measured with the use of a chemiluminescent immunoassay (Immulite; Siemens USA). HOMA-IR was calculated from fasting glucose and insulin (20) and logtransformed for data analyses.

Arterial stiffness

Pulse wave velocity (PWV) and augmentation index (AI) were used as indexes of arterial stiffness. PWV was measured by assessing transcutaneous Doppler flow measurements (Model 806-CB; Parks Medical Electronics) at the right common carotid artery and the right femoral artery (21). Twenty Doppler wave forms were recorded (Windaq software, version 2.31; DATAQ Instruments) at the 2 sites simultaneously. Pulse transit time was determined as the difference in pulse arrival times for the carotid and femoral sites and was based on foot-to-foot comparisons of wave forms from the 2 sites, with the foot being identified as the peak on the second derivative of the pulse wave. The distances between the aorta and the carotid site and the aorta and the femoral site were measured over the skin with the use of the second intercostal space as a landmark for the aorta; the difference between these distances was considered to be the propagation distance (22). PWV for each pulse was calculated as propagation distance in meters divided by transit time in seconds. The mean of the 20 waveforms was used to reflect the PWV for one test.

AI was determined by using applanation tonometry (model no. TCB-500; Millar Instruments) on the common carotid artery (21). At least 20 digital pulse waves were recorded and analyzed with

Windaq software (version 2.31; DATAQ Instruments). The software was used to identify the maximum and minimum voltage on each wave form, with the difference corresponding to pulse pressure. The software also was used to generate the second derivative of the pulse wave, which was used for the identification of the shoulder on the upstroke of the raw wave form. The difference between the peak voltage and the voltage at the shoulder was calculated to reflect augmentation pressure. AI was calculated as AI = 100 × AP/PP, where AP is augmentation pressure and PP is pulse pressure, for each of the 20+ wave-forms, and the resulting values were averaged.

Statistical analyses

The analyses were performed on a per-protocol basis and therefore only included data from subjects who provided follow-up data and were adherent to the intervention (i.e., excluding participants who had little or no weight loss, defined as <1% reduction from baseline). Intention-to-treat analyses were not used because they resulted in differences in weight loss between groups (because of differences in dropout rates and intervention adherence), which is problematic when studying the effects of matched weight loss on outcomes. Baseline characteristics between groups were compared with Fisher's exact tests and ANOVAs. Outcomes were compared by using an ANCOVA, in which the study group was the independent variable, change in the outcome (i.e., final value minus baseline value) was the dependent variable, and the baseline value was a covariate. Between-group post hoc comparisons were performed with the use of the protected F test principle and least significant difference tests. Baseline-adjusted least squares means were used to evaluate the significance of within-group changes. All statistical tests were 2-tailed, and significance was accepted at $P \leq 0.05$. Data are presented as arithmetic means $\pm$ SEs, unless indicated otherwise and except for mean change values, which were adjusted for baseline values. Analyses were performed with the use of SAS for Windows (version 9.3).

Sample sizes of 18 subjects/group were calculated based on the primary outcomes of the parent study (glucose tolerance and insulin action), which were reported previously (14). For selected ancillary outcomes in the present study, we used these sample sizes to calculate the statistical power $(1-\beta)$ to detect meaningful differences in the magnitude of change between groups. Meaningful differences were defined as 10% of the baseline values from our previous study (7). For example, baseline systolic BP was 120 mm Hg; therefore, a change of 12 mm Hg was considered to be meaningful. The inputs for the analyses also included an α of 0.05, 1-tailed tests, and SDs of change scores from our previous study (7). The resulting power values for systolic and diastolic BP; total, LDL, and HDL cholesterol; and triglycerides ranged from 0.79 to 0.99, indicating high power. Serum C-reactive protein concentrations and HOMA-IR were underpowered, with calculated power values of 0.14 and 0.21, respectively.

RESULTS

Participants

A total of 525 individuals inquired about the study. Most ($n = 393$) were not eligible (mostly on the basis of BMI ≥ 30), and

63 were not interested after learning more details about the study requirements. The remaining 69 men and women were enrolled, underwent baseline testing, and were randomly allocated to one of the 3 study groups (**Figure 1**). One participant withdrew immediately after random assignment because of dissatisfaction with her group assignment, and 11 participants withdrew during the intervention for personal reasons ($n = 9$) or medical reasons unrelated to the study ($n = 2$). Data from 5 participants were excluded because these individuals were noncompliant with the interventions (0.5% weight loss to 1.3% weight gain). Therefore, the final data analyses were based on 52 participants; sample sizes for each group are shown in Figure 1 and **Table 1**. None of the demographic or baseline characteristics differed between groups (Table 1).

Weight loss and body composition

By design, weight loss was ~7% in all 3 study groups and did not differ ($P = 0.43$) between groups (CR, 6.8% $\pm$ 0.5%; EX, 7.1% $\pm$ 0.5%; CREX, $-7.6\% \pm 0.4\%$; **Table 2**). The weight change corresponded with an ~15% reduction in fat mass and significant reductions in trunk fat, waist circumference, and waist-to-hip ratio that did not differ between groups (Table 2). Fat-free mass decreased by 2.5% and 1.6% in the CR and CREX groups, respectively (both $P \leq 0.002$), whereas no change was observed in the EX group ($P = 0.56$); however, the between-group comparison of changes did not achieve statistical significance ($P = 0.06$). Body weight did not change significantly in any of the groups during the 2-wk weight stability period that preceded follow-up testing (all $P \geq 0.28$).

Dietary intake

Changes in self-reported energy intake differed significantly between groups ($P = 0.0002$), with the CR ($-32\% \pm 4\%$; $P < 0.0001$) and CREX ($-27\% \pm 4\%$; $P < 0.0001$) groups decreasing significantly and the EX group not changing ($-7\% \pm 4\%$, $P = 0.11$). The results were similar when reported as absolute changes in energy intake (**Table 3**), although the change in the EX group also became significant ($P = 0.004$). For all groups combined, there was a small decrease in the contribution of fat to total energy intake ($P = 0.02$) and a small increase in protein ($P = 0.003$); however, the changes did not differ between groups (Table 3, both between-group P values ≥ 0.54).

Exercise volume, energy expenditure, and aerobic capacity

On the basis of data from the HR monitors used by the participants during exercise, and as reported previously (14), the EX group had a net exercise energy expenditure of 412 $\pm$ 26 kcal/d (22% of baseline TEE), and exercised 8 $\pm$ 1 times/wk for a total weekly exercise duration of 7.4 $\pm$ 0.5 h/wk; mean intensity was 77% $\pm$ 1% of measured maximum HR. For the CREX group, exercise energy expenditure was 217 $\pm$ 23 kcal/d (10% of baseline TEE), exercise frequency was 6 $\pm$ 1 sessions/wk, total weekly exercise time was 4.4 $\pm$ 0.5 h/wk, and the mean intensity was 74% $\pm$ 1% of maximal HR. On the basis of estimates from the PAR and accelerometers, total daily energy expenditure increased in the EX (185 $\pm$ 53 kcal/d, $P = 0.001$) and CREX (126 $\pm$ 48 kcal/d, $P = 0.01$) groups and did not change from baseline in the CR group (-22 ± 51 kcal/d, $P = 0.66$)
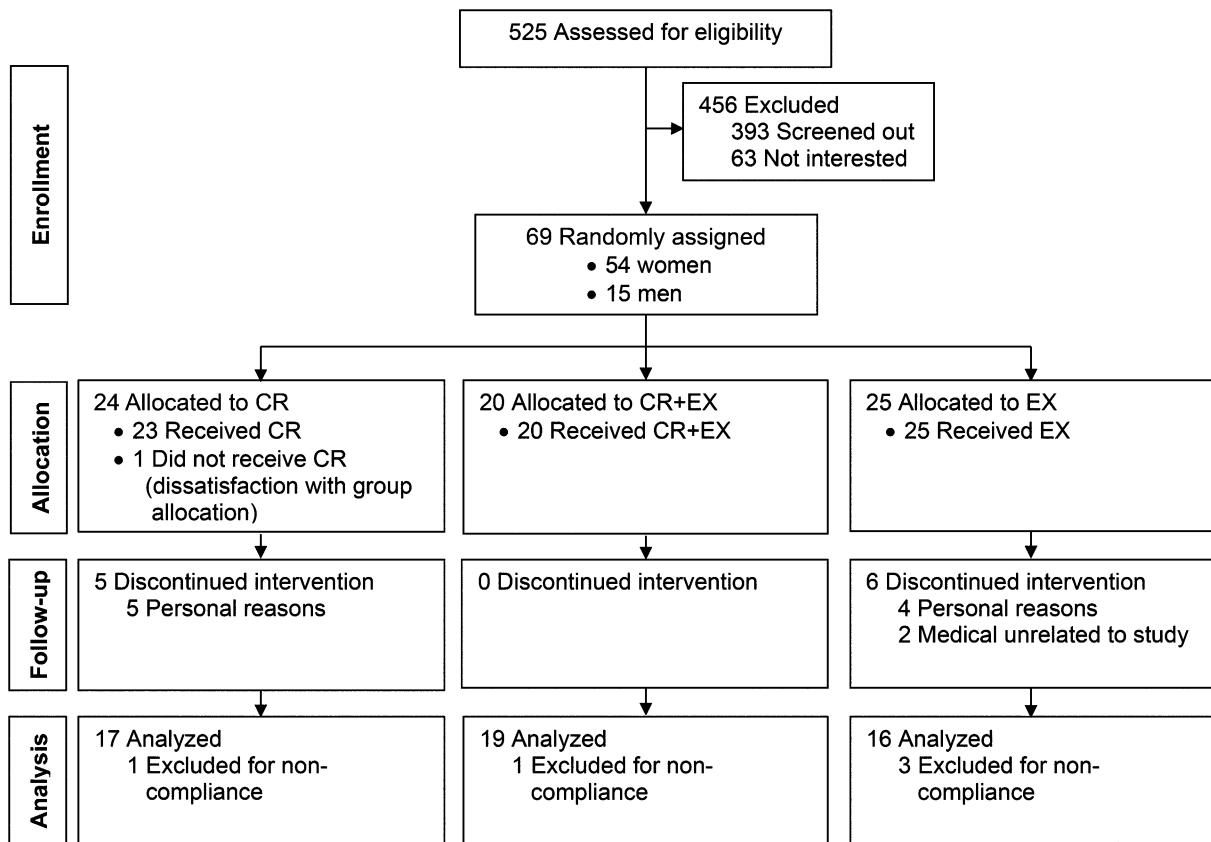
FIGURE 1 Consort diagram indicating sample sizes at each stage during the study. CR, calorie restriction; CR+EX, calorie restriction and exercise combined; EX, endurance exercise training.

(between-group $P = 0.02$). The increases in TEE were less than those for exercise energy expenditure, as expected because of weight loss during the intervention. Sedentary and light physical activity did not change on the basis of the PAR (data not shown; $P \geq 0.19$ for all groups).

VO_{2max} relative to body mass did not change in the CR group ($-1\% \pm 3\%$; $P = 0.85$), whereas moderate and large increases were observed in the CREX group ($11\% \pm 3\%$; $P = 0.0006$) and EX group ($22\% \pm 3\%$; $P < 0.0001$), respectively (between-group $P < 0.0001$; Table 2). When VO_{2max} was expressed in

absolute terms or relative to fat-free mass, the significant difference between groups remained. However, within group, VO_{2max} decreased in the CR group, increased in the EX group, and was unchanged in the CREX group (Table 2).

BP and HR

Mean BP at baseline was below the criteria for prehypertension. Systolic and diastolic BPs decreased when data from all groups were pooled (**Table 4**). There was a tendency for

TABLE 1
Baseline characteristics of study participants[1]

	All	CR	EX	CREX	Between-group P
Participants, n	52	17	16	19	—
Sex, F	39 (75)	13 (76)	11 (69)	15 (79)	0.85
Age, y	57 ± 5	57 ± 5	56 ± 6	57 ± 7	0.86
Race					0.26
Caucasian	42 (81)	16 (94)	12 (75)	14 (74)	
African American	7 (13)	0 (0)	3 (19)	4 (21)	
Other or not specified	3 (6)	1 (6)	1 (6)	1 (5)	
BMI, kg/m^2	27.7 ± 1.7	27.7 ± 1.7	27.0 ± 1.5	28.3 ± 1.8	0.08
Body weight, kg					
Women	75.5 ± 6.9	73.2 ± 5.1	74.2 ± 5.5	77.2 ± 8.6	0.26
Men	92.0 ± 11.5	92.4 ± 7.9	86.3 ± 11.4	98.7 ± 13.5	0.30

[1]Values are means ± SDs for quantitative data and n (%) for categorical data. Between-group P values for quantitative data are from ANOVAs; those for categorical data are from Fisher's exact tests. CR, calorie restriction; CREX; calorie restriction and exercise combined; EX, endurance exercise training.

TABLE 2
Changes in anthropometric measures, body composition, and aerobic capacity in response to weight loss induced by CR, EX, or CREX[1]

	All (n = 52)	CR (n = 17)	EX (n = 16)	CREX (n = 19)	Between-group P
Body mass, kg					
Baseline	79.6 ± 1.5	77.9 ± 2.4	78.1 ± 2.3	82.4 ± 2.9	0.38
Final	73.9 ± 1.4	72.5 ± 2.3	72.6 ± 2.3	76.2 ± 2.8	
Change	5.7 ± 0.2	−5.4 ± 0.4	−5.6 ± 0.4	−6.1 ± 0.4	0.43
Within-group P	<0.0001	<0.0001	<0.0001	<0.0001	
BMI, kg/m^2					
Baseline	27.7 ± 0.2	27.7 ± 0.4	27.0 ± 0.4	28.3 ± 0.4	0.08
Final	25.7 ± 0.2	25.8 ± 0.4	25.1 ± 0.4	26.2 ± 0.4	
Change	−2.0 ± 0.1	−1.9 ± 0.1	−2.0 ± 0.1	−2.1 ± 0.1	0.56
Within-group P	<0.0001	<0.0001	<0.0001	<0.0001	
Waist circumference, cm					
Baseline	92.3 ± 1.3	91.7 ± 2.4	92.4 ± 1.8	92.8 ± 2.5	0.95
Final	84.3 ± 1.4	85.7 ± 2.5	82.6 ± 2.4	84.3 ± 2.7	
Change	−7.8 ± 0.9	−6.9 ± 1.4	−9.8 ± 1.5	−6.5 ± 1.5	0.25
Within-group P	<0.0001	<0.0001	<0.0001	0.0001	
Waist:hip circumference ratio					
Baseline	0.85 ± 0.01	0.83 ± 0.02	0.86 ± 0.02	0.86 ± 0.02	0.53
Final	0.82 ± 0.01	0.82 ± 0.02	0.83 ± 0.02	0.82 ± 0.02	
Change	−0.02 ± 0.01	−0.02 ± 0.1	−0.02 ± 0.01	−0.03 ± 0.1	0.93
Within-group P	<0.0001	0.03	0.03	0.02	
Total fat mass, kg					
Baseline	32.1 ± 0.7	32.2 ± 1.1	30.4 ± 1.3	33.4 ± 1.3	0.24
Final	27.4 ± 0.7	28.1 ± 1.1	25.5 ± 1.4	28.3 ± 1.2	
Change	−4.7 ± 0.2	−4.1 ± 0.3	−4.9 ± 0.3	−5.0 ± 0.3	0.10
Within-group P	<0.0001	<0.0001	<0.0001	<0.0001	
Total fat, %					
Baseline	42.1 ± 0.8	43.5 ± 1.7	40.5 ± 1.4	42.2 ± 1.0	0.34
Final	38.7 ± 0.9	40.7 ± 1.8	36.4 ± 1.6	38.7 ± 1.1	
Change	−3.5 ± 0.2	−2.8 ± 0.4	−4.0 ± 0.4	−3.6 ± 0.3	0.07
Within-group P	<0.0001	0.06	0.002	0.05	
Total fat-free mass, kg					
Baseline	47.1 ± 1.3	45.2 ± 2.5	47.4 ± 1.9	48.6 ± 2.1	0.55
Final	46.4 ± 1.2	44.2 ± 2.4	47.2 ± 2.0	47.7 ± 2.0	
Change	−0.7 ± 0.2	−1.1 ± 0.3	−0.2 ± 0.3	−0.8 ± 0.3	0.06
Within-group P	<0.0001	0.0002	0.56	0.002	
Trunk fat mass, kg					
Baseline	16.9 ± 0.5	17.4 ± 0.8	15.7 ± 1.0	17.4 ± 1.0	0.35
Final	14.1 ± 0.5	15.0 ± 0.7	12.9 ± 1.0	14.3 ± 0.9	
Change	−2.8 ± 0.2	−2.4 ± 0.3	−2.9 ± 0.3	−3.0 ± 0.3	0.23
Within-group P	<0.0001	<0.0001	<0.0001	<0.0001	
Trunk fat, %					
Baseline	43.9 ± 0.8	45.9 ± 1.5	41.9 ± 1.5	43.7 ± 1.2	0.15
Final	39.4 ± 1.0	42.4 ± 1.8	36.9 ± 1.8	39.0 ± 1.3	
Change	−4.4 ± 0.3	−3.7 ± 0.5	−4.8 ± 0.5	−4.7 ± 0.5	0.27
Within-group P	<0.0001	<0.0001	<0.0001	<0.0001	
VO$_{2max}$ relative to body mass, mL · kg^{-1} · min^{-1}					
Baseline	25.0 ± 0.8	26.4 ± 1.5	25.4 ± 1.3	23.5 ± 1.2	0.29
Final	27.5 ± 1.0	26.5 ± 1.9	30.7 ± 1.7	25.6 ± 1.5	
Change	2.6 ± 0.5	−0.1 ± 0.8[a]	5.3 ± 0.8[b]	2.6 ± 0.7[c]	<0.0001
Within-group P	<0.0001	0.85	<0.0001	0.0009	
VO$_{2max}$ relative to fat-free mass, mL · kg^{-1} · min^{-1}					
Baseline	42.6 ± 1.2	46.2 ± 2.0	41.9 ± 2.3	40.1 ± 1.8	0.09
Final	44.0 ± 1.3	43.3 ± 2.2	47.8 ± 2.6	41.3 ± 1.9	
Change	1.4 ± 0.8	−2.8 ± 1.2[a]	5.8 ± 1.1[b]	1.2 ± 1.1[c]	<0.0001
Within-group P	0.09	0.02	<0.0001	0.28	
Absolute VO$_{2max}$, mL/min					
Baseline	2000 ± 79	2112 ± 158	1985 ± 127	1914 ± 127	0.81
Final	2046 ± 88	1960 ± 177	2252 ± 148	1939 ± 131	
Change	46 ± 40	−124 ± 59[a]	289 ± 58[b]	64 ± 59[c]	<0.0001
Within-group P	0.26	0.04	<0.0001	0.28	

[1] Values are arithmetic means ± SEs, except for change values, which are least squares means ± SEs that have been adjusted for differences in baseline values between groups. Between-group P values reflect the significance of the between-group differences in change values after adjustment for baseline values with the use of ANCOVA. Labeled means in a row without a common superscript letter are significantly different, $P < 0.05$. CR, calorie restriction; CREX, calorie restriction and exercise combined; EX, endurance exercise training; VO$_{2max}$, maximal oxygen consumption as an index of aerobic capacity.

TABLE 3
Energy and macronutrient intake in response to CR, EX, or CREX[1]

	All (n = 52)	CR (n = 17)	EX (n = 16)	CREX (n = 19)	Between-group P
Total energy, kcal/d					
Baseline	2165 ± 85	2243 ± 137	1908 ± 125	2310 ± 159	0.12
Final	1610 ± 62	1428 ± 85	1781 ± 115	1630 ± 107	
Change	−554 ± 84	−764 ± 93[a]	−295 ± 98[b]	−585 ± 89[a]	0.005
Within-group P	<0.0001	<0.0001	0.004	<0.0001	
Carbohydrate, % of energy					
Baseline	48 ± 1	44 ± 2[a]	47 ± 2[a]	51 ± 2[b]	0.04
Final	48 ± 1	47 ± 2	49 ± 2	49 ± 2	
Change	1 ± 1	1 ± 2	2 ± 2	0 ± 2	0.76
Within-group P	0.65	0.77	0.39	0.86	
Fat, % of energy					
Baseline	36 ± 1	37 ± 2	37 ± 2	33 ± 2	0.14
Final	33 ± 1	33 ± 1	34 ± 2	31 ± 2	
Change	−3 ± 1	−3 ± 2	−2 ± 2	−3 ± 2	0.87
Within-group P	0.02	0.04	0.19	0.11	
Protein, % of energy					
Baseline	16 ± 1	17 ± 1	15 ± 1	15 ± 1	0.50
Final	18 ± 1	19 ± 1	17 ± 1	17 ± 1	
Change	2 ± 1	3 ± 1	1 ± 1	2 ± 1	0.54
Within-group P	0.003	0.008	0.25	0.09	

[1] Values are arithmetic means ± SEs, except for change values, which are least squares means ± SEs that have been adjusted for differences in baseline values between groups. Between-group P values reflect the significance of the between-group differences in change values after adjustment for baseline values with the use of ANCOVA. Labeled means in a row without a common superscript letter are significantly different, P < 0.05. CR, calorie restriction; CREX, calorie restriction and exercise combined; EX, endurance exercise training.

differences between groups (P = 0.07) for systolic BP, with reductions in the CR (P = 0.0002) and CREX (P = 0.01) groups, whereas the EX group did not change (P = 0.63). Diastolic BP decreased in all groups, and there was no difference in the magnitude of improvement between groups. Resting HR decreased slightly when data from all groups were pooled (Table 4). However, there were no differences between groups.

Plasma lipids

Total, LDL, and non-HDL cholesterol concentrations decreased significantly (all P < 0.01) and to a similar extent in the 3 study groups (all between-group P values ≥ 0.26) (Table 4). HDL cholesterol concentrations did not change (P = 0.30), nor were there between-group differences in HDL cholesterol responses to the interventions (P = 0.19). The ratio of total to HDL cholesterol decreased with all groups combined, and there were no differences between groups for the magnitude of change. Triglyceride concentrations decreased by 16% for all groups combined and there were no significant differences between groups (P = 0.12).

Glucose, insulin, and C-reactive protein

Fasting plasma glucose concentrations decreased by 3% from baseline (P = 0.0003), and fasting insulin decreased by 25% (P < 0.0001). This resulted in a 70% reduction in the HOMA-IR index (Table 4). There were no differences between groups for glucose, insulin, or HOMA-IR index (all P ≥ 0.28). C-reactive protein did not change.

Arterial stiffness

PWV and AI did not change with weight loss, nor were there differences in PWV or AI between groups (**Table 5**). Because these measures are susceptible to confounding by BP and HR, we also performed analyses in which the changes in BP and HR were included as covariates. However, this did not change the findings (data not shown). Furthermore, we adjusted the AI values to a standardized HR of 75 beats/min on the basis of the inverse relation between AI and HR of 4.8 AI units per HR of 10 beats/min (23, 24), and, again, the findings were not altered (Table 5).

DISCUSSION

Reductions in energy intake and increases in energy expenditure result in weight loss, which has well-known health benefits. However, dietary changes and exercise training also have benefits that are not directly attributable to weight loss (8–13). In this context, we hypothesized that CREX would yield greater improvements in risk factors for CVD than would similar weight loss from CR or EX alone. However, the results did not support this hypothesis. Substantial improvements were observed for most of the risk factors; on the basis of published algorithms (25) these changes would be expected to lower the lifetime risk of developing CVD from 46% to 36%. However, contrary to our expectations, the magnitude of improvement did not depend on whether CR, EX, or CREX was used to promote weight loss. This finding is in contrast to the additive effects of CR and EX on insulin action that we recently reported elsewhere (14).

Two other studies evaluated the independent and combined effects of CR and EX (26, 27). However, in these studies, the exercise interventions did not provide meaningful weight loss,

TABLE 4
Changes in BP and serum lipid concentrations in response to weight loss induced by CR, EX, or CREX[1]

	All (n = 52)	CR (n = 17)	EX (n = 16)	CREX (n = 19)	Between-group P
Systolic BP, mm Hg					
Baseline	117 ± 2	121 ± 3	112 ± 2	119 ± 2	0.04
Final	112 ± 2	111 ± 3	112 ± 3	114 ± 3	
Change	−5 ± 1	−8 ± 2[a]	−1 ± 2[b]	−5 ± 2[ab]	0.07
Within-group P	0.0004	0.0002	0.63	0.01	
Diastolic BP, mm Hg					
Baseline	75 ± 1	75 ± 2	73 ± 2	77 ± 2	0.40
Final	72 ± 1	72 ± 2	71 ± 2	72 ± 2	
Change	−4 ± 1	−3 ± 1	−3 ± 1	−5 ± 1	0.63
Within-group P	0.0008	0.05	0.03	0.001	
Resting heart rate, beats/min					
Baseline	69 ± 1	68 ± 2	66 ± 1	72 ± 2	0.02
Final	66 ± 1	66 ± 2	64 ± 2	68 ± 2	
Change	−3 ± 1	−2 ± 2	−3 ± 2	−3 ± 2	0.90
Within-group P	0.02	0.27	0.11	0.11	
Total cholesterol, mg/dL					
Baseline	200 ± 5	202 ± 7	191 ± 7	206 ± 9	0.41
Final	183 ± 3	186 ± 5	181 ± 6	181 ± 6	
Change	−17 ± 4	−15 ± 5	−14 ± 5	−22 ± 4	0.39
Within-group P	<0.0001	0.002	0.007	<0.0001	
LDL cholesterol, mg/dL					
Baseline	122 ± 4	119 ± 7	117 ± 5	127 ± 8	0.58
Final	109 ± 3	110 ± 6	107 ± 5	111 ± 6	
Change	−12 ± 3	−10 ± 4	−12 ± 4	−14 ± 3	0.81
Within-group P	0.007	0.007	0.003	0.0003	
HDL cholesterol, mg/dL					
Baseline	56 ± 2	60 ± 4	54 ± 4	55 ± 4	0.52
Final	55 ± 2	55 ± 4	56 ± 5	53 ± 3	
Change	−1 ± 1	−4 ± 2	2 ± 2	−2 ± 2	0.19
Within-group P	0.30	0.09	0.39	0.36	
Non-HDL cholesterol, mg/dL					
Baseline	144 ± 5	142 ± 9	137 ± 7	151 ± 10	0.53
Final	128 ± 4	131 ± 7	125 ± 6	128 ± 7	
Change	−16 ± 3	−12 ± 4	−14 ± 4	−20 ± 4	0.26
Within-group P	<0.0001	0.004	0.001	<0.0001	
Total-to-HDL cholesterol ratio					
Baseline	3.9 ± 0.2	3.7 ± 0.3	3.8 ± 0.3	4.1 ± 0.4	0.62
Final	3.6 ± 0.1	3.6 ± 0.3	3.5 ± 0.2	3.7 ± 0.3	
Change	−0.3 ± 0.1	−0.1 ± 0.1	−0.3 ± 0.1	−0.4 ± 0.1	0.24
Within-group P	0.002	0.22	0.004	0.0007	
Triglycerides, mg/dL					
Baseline	111 ± 9	114 ± 12	97 ± 15	121 ± 20	0.58
Final	93 ± 7	106 ± 11	93 ± 14	83 ± 10	
Change	−18 ± 8	−7 ± 9	−13 ± 10	−32 ± 9	0.12
Within-group P	0.03	0.47	0.21	0.0007	
Fasting glucose, mg/dL					
Baseline	96 ± 1	97 ± 2	94 ± 2	97 ± 3	0.48
Final	93 ± 1	94 ± 1	92 ± 1	92 ± 2	
Change	−3 ± 1	−3 ± 1	−2 ± 1	−4 ± 1	0.28
Within-group P	0.0003	0.03	0.09	0.0001	
Fasting insulin, μU/mL					
Baseline	8.3 ± 0.8	8.2 ± 1.0	8.6 ± 1.6	8.2 ± 1.5	0.98
Final	6.3 ± 0.7	5.9 ± 0.6	7.1 ± 1.7	5.9 ± 1.1	
Change	−2.1 ± 0.3	−2.3 ± 0.5	−1.4 ± 0.5	−2.4 ± 0.5	0.28
Within-group P	<0.0001	<0.0001	0.006	<0.0001	
Log HOMA-IR					
Baseline	0.46 ± 0.09	0.51 ± 0.16	0.46 ± 0.15	0.41 ± 0.18	0.92
Final	0.14 ± 0.09	0.21 ± 0.12	0.22 ± 0.17	0.01 ± 0.18	
Change	−0.32 ± 0.05	−0.29 ± 0.08	−0.25 ± 0.08	−0.41 ± 0.08	0.31
Within-group P	<0.0001	0.0008	0.005	<0.0001	

(Continued)

TABLE 4 (*Continued*)

	All (*n* = 52)	CR (*n* = 17)	EX (*n* = 16)	CREX (*n* = 19)	Between-group *P*
C-reactive protein, mg/L					
Baseline	2.0 ± 0.2	2.5 ± 0.5	1.7 ± 0.3	1.8 ± 0.4	0.34
Final	1.6 ± 0.2	2.0 ± 0.3	1.4 ± 0.3	1.6 ± 0.3	
Change	−0.3 ± 0.2	−0.2 ± 0.3	−0.5 ± 0.3	−0.3 ± 0.3	0.80
Within-group *P*	0.10	0.47	0.10	0.25	

[1] Values are arithmetic means ± SEs, except for change values, which are least squares means ± SEs that have been adjusted for differences in baseline values between groups. Between-group *P* values reflect the significance of the between-group differences in change values after adjustment for baseline values with the use of ANCOVA. Labeled means in a row without a common superscript letter are significantly different, *P* < 0.05. The exclusion of 2 participants who had changes in anti-inflammatory medications did not alter the results for C-reactive protein. BP, blood pressure; CR, calorie restriction; CREX, calorie restriction and exercise combined; EX, endurance exercise training.

and the magnitude of weight loss differed between groups, making it difficult to determine whether the observed changes in risk factors were attributable to weight loss or to weight loss–independent effects. Furthermore, in a previous study, we showed that matched, yearlong weight losses from CR and EX had similar beneficial effects on CVD risk factors (7); however, additive effects could not be evaluated because there was not a group that underwent CREX. To our knowledge, the present study is the first to compare the independent and combined effects of CR and EX with matched weight loss.

A straightforward interpretation of the findings from the present study is that weight loss itself provides the major cardioprotective effect of CREX and that the benefits do not depend on which approach to weight loss is used. However, 3 issues related to this notion warrant consideration. First, although the physiologic mechanisms are not clear, the cardioprotective effects of exercise are not necessarily mediated by changes in CVD risk factors. Accordingly, a sedentary lifestyle and low aerobic capacity increase CVD risk by 50–100%, even after accounting for other risk factors (28, 29). Therefore, despite the fact that the

EX and CREX groups did not have greater improvements in BP, lipids, glucose, and body composition, these groups would be at lower risk of CVD because they were no longer sedentary and because of the increases in VO_{2max}. Second, because adiposity is an independent risk factor for CVD (30), the small nonsignificant tendency for greater fat mass reductions (and preservation of fat-free mass), may confer an advantage for exercise-induced weight loss. Third, because the study was designed for matched weight losses in the 3 study groups, the degree of CR and the amount of EX was less in the CREX group than it was in the CR and EX groups, respectively. Accordingly, the weight loss–independent benefits of CR and EX may have been lower. If the CR and EX doses were matched, it is plausible that the changes in CVD risk factors would have been greater in the CREX group; however, it would not be possible to distinguish the CR- and EX-specific effects from the greater weight loss that also would occur in this scenario.

The magnitude of weight loss in the present study (∼7%) was modest and was not sufficient for the mean BMI to reach optimal values. Despite this, the benefits were relatively large.

TABLE 5
Indexes of arterial stiffness, as measured before and after weight loss[1]

	All (*n* = 52)	CR (*n* = 17)	EX (*n* = 16)	CREX (*n* = 19)	Between-group *P*
Pulse wave velocity, m/s					
Baseline	7.2 ± 0.5	7.7 ± 0.8	7.2 ± 1.1	6.8 ± 0.5	0.74
Final	6.6 ± 0.5	7.3 ± 1.1	6.2 ± 0.5	6.5 ± 0.7	
Change	−0.6 ± 0.6	−0.1 ± 0.8	−1.1 ± 0.8	−0.7 ± 0.8	0.66
Within-group *P*	0.30	0.92	0.17	0.39	
Augmentation index, %					
Baseline	21 ± 2	19 ± 4	21 ± 4	23 ± 2	0.66
Final	21 ± 2	21 ± 4	21 ± 4	19 ± 4	
Change	0 ± 2	1 ± 3	1 ± 3	−3 ± 3	0.60
Within-group *P*	0.84	0.68	0.86	0.36	
Augmentation index corrected for heart rate					
Baseline	18 ± 2	16 ± 4	16 ± 4	22 ± 2	0.34
Final	16 ± 2	17 ± 4	16 ± 4	15 ± 4	
Change	−2 ± 2	1 ± 3	−1 ± 3	−5 ± 3	0.49
Within-group *P*	0.40	0.85	0.82	0.15	

[1] Values are arithmetic means ± SEs, except for change values, which are least squares means ± SEs that have been adjusted for differences in baseline values between groups. Between-group *P* values reflect the significance of the between-group differences in change values after adjustment for baseline values with the use of ANCOVA. Values for augmentation index corrected for heart rate were adjusted to a standardized heart rate of 75 beats/min based on published recommendations (23, 24). CR, calorie restriction; CREX, calorie restriction and exercise combined; EX, endurance exercise training.

However, larger and longer-term weight loss would likely produce even greater benefits. For example, middle-aged individuals undergoing self-imposed CR for a mean of 6 y (BMI 19.6 ± 0.4) had LDL cholesterol concentrations of 86 ± 5 mg/dL, HDL cholesterol concentrations of 65 ± 7 mg/dL, triglyceride concentrations of 54 ± 4 mg/dL, and systolic and diastolic BPs of 97 ± 2 and 59 ± 1 mm Hg (31), respectively, which corresponds with a predicted lifetime CVD risk of 5% (25). All of these are substantially better than the corresponding postintervention values from the present study (LDL cholesterol: 109 ± 3 mg/dL; HDL cholesterol: 55 ± 2 mg/dL; triglycerides: 93 ± 7 mg/dL; BP: 112 ± 2/72 ± 1 mm Hg; and lifetime CVD risk: 36%). Exercise interventions of longer duration also may have greater effects than those observed in the present study. For example, HDL cholesterol does not appear to change significantly until ≥9 mo of EX has been completed (32). Furthermore, whereas 1 y of training increased HDL cholesterol concentrations from 38 ± 3 mg/dL to 45 ± 4 mg/dL in patients with CVD, 7 y of training increased their HDL cholesterol concentrations further, to 53 ± 5 mg/dL (33).

Arterial stiffness increases throughout the adult life span (34, 35), largely because of changes in elastin and collagen in the extracellular matrix of the arterial wall (36). Although increasing age and high BP are strongly associated with arterial stiffness (37, 38), they are also associated with an increased risk of CVD mortality, even after accounting for these and other CVD risk factors (39). We included carotid–femoral PWV and AI as measures of arterial stiffness in the present study and neither changed significantly. In a recent review and meta-analysis, it was found that 8 other weight loss studies also reported no effect of weight loss on carotid–femoral PWV, whereas 12 studies did observe beneficial effects. With all 20 studies pooled, the results indicated that a mean weight loss of 8% results in a statistically and clinically significant PWV reduction (improvement) of 0.6 m/s (40). This suggests that large sample sizes may be needed to reliably detect significant changes in PWV. Interestingly, we also observed a 0.6 m/s reduction in PWV (all groups combined), albeit not significant, perhaps because of the small sample size.

Our study has limitations. First, CVD risk factors were measured as surrogates for hard outcomes, such as myocardial infarction or CVD mortality. However, studies that have evaluated hard outcomes have had trouble producing long-term weight loss (41); therefore, they cannot provide definitive information about the effects of successful weight loss on hard CVD outcomes. Second, the eligibility criteria were selected to ensure a homogeneous population that would tolerate the intervention, and to avoid the confounding effects of medical or other conditions. However, this limits the generalizability of the findings. Lastly, the differences in CVD risk outcomes between groups may have been nonsignificant because of an inadequate sample size. However, with the exception of triglycerides, there were no statistical trends for the additive effects of CR and EX. Furthermore, for most outcomes, the improvements in the CREX group were only modestly greater than in the other groups and would be of questionable clinical significance if they were statistically significant. For example, the decrease in LDL cholesterol in the CREX group was only 2–4 mg/dL better than that in the other groups, and the reduction in diastolic BP was only 2 mm Hg greater than that in the other groups.

In conclusion, the results from this study indicate that matched 7% weight losses from CR, EX, or CREX have similar but substantial beneficial effects on BP, plasma lipids, and fasting blood glucose. These findings suggest that the weight loss–independent effects of CR and EX on risk factors for CVD are not additive. However, because a sedentary lifestyle and poor aerobic capacity are independent risk factors for CVD, EX provides a benefit that cannot be achieved by using CR alone; therefore, EX remains as a critical component of CVD risk reduction programs. The evidence from this study adds to that from a multitude of studies, which clearly indicate that weight loss has powerful effects to improve the CVD risk profile. Accordingly, continued research and programs are needed to promote long-term adherence to weight loss for the general population.

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