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ORIGINAL RESEARCH

Predictors of Improvement in Cardiometabolic Risk Factors With Weight Loss in Women

Caitlin A. Dow, PhD; Cynthia A. Thomson, PhD, RD; Shirley W. Flatt, MS; Nancy E. Sherwood, PhD; Bilge Pakiz, EdD; Cheryl L. Rock, PhD, RD

***Background*—**Weight loss is associated with improvements in cardiometabolic risk factors, including serum glucose, insulin, C-reactive protein, and blood lipids. Few studies have evaluated the long-term (>18 months) effect of weight loss on these risk factors or sought to identify factors associated with sustained improvements in these measures.

***Methods and Results*—**In 417 overweight/obese women (mean [SD] age, 44 [10] years) participating in a weight loss trial, we sought to identify predictors of weight loss–associated cardiometabolic risk factors after 12 and 24 months of intervention. Total cholesterol (TC), low-density lipoprotein (LDL)–cholesterol (LDL-C), high-density lipoprotein (HDL)–cholesterol, non-HDL-cholesterol, triglycerides (TG), insulin, glucose, C-reactive protein (CRP), and cardiopulmonary fitness were measured at baseline and at 12 and 24 months. After 24 months, significant reductions in body weight, waist circumference, CRP, TC, HDL-cholesterol, and non-HDL-cholesterol were observed ($P<0.01$). After 24 months, mean TC and non-HDL-cholesterol were reduced regardless of the amount of weight lost, whereas reductions in LDL–cholesterol, CRP, insulin, and TG were observed only in those who lost ≥10% body weight. Step-test performance improved only in those who lost ≥10% body weight after 24 months. Change in weight demonstrated a positive predictive value for change in cholesterol, insulin, glucose, and triglycerides. Baseline level of the biomarker showed the greatest predictive value for follow-up measures for insulin, cholesterol, glucose, and triglycerides.

***Conclusions*—**Our data extend the results from short-term weight loss trials and suggest that the magnitude of weight loss and baseline values for risk factors are associated with improvements in cardiometabolic risk factors even after 24 months.

***Clinical Trials Registration Information*—**URL: http://www.clinicaltrials.gov/. Unique identifier: NCT00640900. **(*J Am Heart Assoc*. 2013;2:e000152 doi: 10.1161/JAHA.113.000152)**

Key Words: lipids • obesity • risk factors • women

Obesity remains a significant risk factor for disease-associated morbidity and mortality in the United States, including that associated with diabetes, coronary heart disease, and stroke.[1] Obese individuals often present with elevated fasting values of glucose,[2] lipids,[1] and inflammatory markers,[2] as well as insulin resistance.[3] Even with modest weight loss, individuals may demonstrate significant improvements in metabolic risk factors for obesity-related disease, particularly cardiovascular disease and diabetes.[1,4–6] It is estimated that a 10% reduction in body weight in an obese individual can promote significant reductions in metabolic parameters including circulating glucose, insulin, and inflammatory markers, even if the body mass index (BMI) remains within an at-risk category.[7] Yet few studies have evaluated this relationship beyond 12 months.

The ability to promote weight loss through dietary interventions is well established, and behavioral weight loss programs and counseling remain a primary clinical approach to reduce body weight in overweight and obese adults.[6] These programs vary in intensity, delivery approach, behavioral constructs applied, dietary plan, and duration. But independent of the approach, energy deficit can be achieved and is associated with modest weight loss.[3,5,8] Further, the demonstrated weight loss associated with targeted dietary interventions generally translates to improvements in metabolic indices related to obesity-associated disease.[4,6,9–11]

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In a recently conducted randomized, controlled weight loss study,[12] women were randomized to receive a structured weight loss program delivered either in person or via telephone or to receive minimal diet counseling, considered usual care, for a period of 24 months. Women assigned to the structured weight loss program arms demonstrated greater reductions in body weight, BMI, and waist circumference over time than those in the usual care condition. More than 70% of women had sustained weight loss at 24 months; the variance in weight loss afforded an opportunity to evaluate the relationship between weight loss and modification of cardiometabolic risk factors. Changes in lipids and C-reactive protein (CRP) according to study arm assignment have been previously reported.[12] Overall, blood lipids did not change in those randomized to the structured weight loss plan, although CRP values were significantly reduced after 12 and 24 months of intervention.[12] The purpose of this analysis was to assess changes in these and additional cardiometabolic risk factors associated with weight loss. Further, this analysis sought to determine which factors (baseline value of biomarker, baseline weight, percent change in body weight, age, race/ethnicity) predicted improvement in cardiometabolic risk factors at 12 and 24 months, independent of treatment arm.

Methods

Study Subjects and Recruitment

The weight loss intervention trial recruited 446 overweight/obese women from a screened sample of 564 women. Women were eligible to participate if they were >18 years of age, had a BMI between 25 and 40 kg/m^2, and were a minimum of 15 kg above ideal body weight as defined by the 1983 Metropolitan Life tables.[13] Participants were recruited via listservs and flyers distributed through each of the 4 study sites (University of California, San Diego; University of Arizona, Tucson; University of Minnesota, Minneapolis; and Kaiser Permanente Center Northwest). Any woman who was pregnant, planning a pregnancy, lactating, reported a history of eating disorders, other psychiatric disorders, comorbid conditions, or food allergies, or was unable to perform a 3-minute step test for cardiopulmonary fitness assessment was excluded from enrollment. All study participants completed the consent process and provided written informed consent prior to randomization. The institutional review boards approved this study for Human Subjects' Protection at each recruitment site prior to study initiation.

Intervention

The details of the study participation have been previously described.[12] Briefly, all women enrolled in the trial received weight loss counseling. Eligible women were randomized in a 3:3:2 allocation to center-based, telephone-based, or usual care that included weight loss counseling by a dietetics professional. Women in the center-based intervention arm visited the weight loss center weekly for brief counseling sessions and weigh-ins with designated trained staff; they also had access to Web-based resource materials. Women in the telephone-based arm similarly received weekly counseling by telephone to reinforce weight loss behaviors and goals. They also had access to Web-based resource materials. Prepackaged meals and snacks provided 42% to 68% of total energy needs of the prescribed eating plan and were provided free of charge for participants randomized to these 2 study arms. Generally, after the initial 12-month period, women were transitioned to fewer prepackaged meals and more self-selected food items. In addition to the prepackaged foods, women assigned to the weight loss program received one-on-one counseling to promote adherence to a low-fat (20% to 30% total energy), reduced-energy (1200 to 2000 kcal), high fruit-and-vegetable eating plan with recommendations for increased physical activity to achieve current guidelines[14] of 30 minutes of planned exercise ≥5 days/week. Usual-care counseling sessions took place once at baseline and again at 6 months. Usual-care study participants received written educational materials to support their dietary goals (500 to 1000 kcal/day deficit); regular physical activity was also promoted. For these analyses treatment arms were collapsed.

Outcomes

The primary outcome of this study was change in cardiometabolic risk factors. Subjects provided a fasting blood sample at baseline and after 12 and 24 months for evaluation of cardiometabolic risk factors. Specifically, fasting plasma was sampled to measure lipid profiles including total cholesterol, triglycerides, and high-density lipoprotein (HDL) using enzymatic methods (Kodak Ektachem Analyzer System; Johnson & Johnson Clinical Diagnostics). Low-density lipoprotein (LDL) was calculated using the Friedewald equation.[15] Non-HDL-cholesterol (non-HDL-C) was calculated by subtracting HDL from the total cholesterol value. Blood glucose was determined using enzymatic methods (Kodak Ektachem DT60 Analyzer; Johnson & Johnson). A double-antibody radioimmunoassay, with <0.2% cross-reactivity with human proinsulin, was used for the analysis of fasting serum insulin (Linco Research Inc). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by dividing the product of fasting glucose (in milligrams per deciliter) and fasting insulin (in microunits per milliliter) by 405.[16] CRP was quantified using a high-sensitivity polystyrene-enhanced turbidimetric in vitro immunoassay kit (DiaSorin Inc).

Secondary outcomes included weight, height, BMI (weight in kilograms/height in meters squared) as well as waist and hip circumference, which were measured at baseline and every 6 months throughout the 24-month study period. In addition, a 3-minute step test was administered at baseline and repeated at 12 and 24 months. This test measures heart rate during the first 30 seconds of recovery from stepping.

Statistical Analysis

Risk categories for cardiometabolic outcomes, used as cut points in tabulation, were identified as follows: glucose (cut point, 100 mg/dL),[17] insulin (cut point, 15 μU/mL),[18] HOMA-IR (cut point, 3.0),[16] CRP (low risk, <1 mg/L; medium risk, 1 to 2.99 mg/L; high risk, ≥3.0 mg/L),[19] total cholesterol (cut point, 200 mg/dL),[17] LDL-cholesterol (cut point, 130 mg/dL),[20] non-HDL-C (cut point, 160 mg/L),[21] HDL-cholesterol (cut point, 60 mg/dL),[17] triglycerides (cut point, 150 mg/dL),[17] waist (cut point, 88 cm),[22] and waist-to-height ratio (cut point, 0.5).[23] Cardiopulmonary fitness recovery heart rate categories for ages <30, 30 to 39, 40 to 59, and ≥50 years were based on literature.[24] Logarithmic transformations were applied in all analyses to improve normality of skewed distributions with the exception of the β coefficients reported in Table 2.

Longitudinal analyses were limited to the 417 women who provided at least 1 follow-up blood sample at either 12 or 24 months. Differences in biochemical risk factors between baseline and each of 12 and 24 months (overall and stratified by a priori biomarker risk category) were analyzed using longitudinal mixed models, controlled for intervention group. Likelihood ratio tests explored interactions between risk strata and time. Each model tested for differences over time and included a subject-specific intercept as a random effect. Regression models predicted laboratory values after 12 and 24 months of study participation as a function of race/ethnicity, age, baseline levels of laboratory analyte, waist circumference, weight change, randomization assignment, cardiorespiratory fitness, and waist-to-height ratio. For each term in each model, we present parameter estimates (β coefficients). To further explore the relationship between change in body weight and cardiometabolic risk factors, stratified analyses, applying a priori clinical cut points for weight loss, were conducted using longitudinal mixed models in which women were classified as either losing ≥10% of baseline body weight or losing <10% of baseline body weight at each of the 12- and 24-month points. Models were controlled for intervention group assignment and tested for interaction between the weight loss categories and biomarker change. In consideration of multiple comparisons issues, statistical significance was set at $P<0.01$. Analyses were conducted using SAS version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Four hundred and forty-six overweight/obese women were enrolled; 4 were removed from analysis because of postrandomization exclusions and 25 did not provide a blood sample at either 12 or 24 months, leaving 417 in the study sample. Table 1 provides baseline demographic characteristics of the study population. Women enrolled in the study were a mean (SD) age of 44 (10) years, had a mean weight of 92.1 (10.8) kg with a BMI of 33.9 (3.4) kg/m^2, and had a waist circumference of 108.6 (9.5) cm. At baseline, 159 women (36%) were postmenopausal. At follow-up, mean weight loss as a percentage of baseline weight was 8.6% (0.4%) in 417 subjects with available measured body weight at 12 months and 6.6% (0.5%) in 407 subjects with weight data at 24 months; 85% and 74% of women had any weight loss at 12 and 24 months, respectively. At study entry, 2 women were using hypoglycemic agents, and 1% of the women (n=5) were using them at study end. Twenty-six subjects took lipid-lowering drugs at study entry and 30 women took them at 24 months; 17 women reported estrogen use throughout the study (data not shown).

As shown in Table 2, several predictors of change in cardiometabolic biomarkers were identified although neither age nor race/ethnicity showed an association. Most relevant was the strong and significant association between percent body weight reduction and change in biomarkers, such that for every 10% point reduction in body weight, there was an estimated 4-point reduction in insulin and glucose, a 5.4 mg/dL reduction in cholesterol, and an 18 mg/dL decrease in serum triglycerides. Baseline level of each biomarker was

Table 1. Baseline Characteristics of Overweight/Obese Women Enrolled in a 24-Month Weight Loss Study (n=442)

Characteristic	Baseline Value, Mean (SD)
Age, y	44 (10)
Weight, kg	92.1 (10.8)
Height, cm	164.9 (6.3)
BMI, kg/m^2	33.9 (3.4)
Waist circumference, cm	108.6 (9.5)
Hip circumference, cm	120.2 (8.2)
Waist-to-hip ratio	0.9 (0.06)
Postmenopausal, n (%)	159 (36)
Education, n	
High school or less	52
Some college	189
College graduate	95
Graduate school	106

BMI indicates body mass index; SD, standard deviation.

Table 2. Predictors of Cardiometabolic Biomarker Values After 12 and 24 Months of Weight Loss Study Participation

	Models Predicting 12-Month Biomarker Values (n=406)				
	Insulin (R^2=0.37)	Cholesterol (R^2=0.46)	Glucose (R^2=0.26)	TG (R^2=0.66)	CRP (R^2=0.16)
Baseline level of biomarker	0.551**	0.597**	0.786**	0.752**	0.470**
Baseline weight	−0.057	−0.093	0.069	0.286	0.041
Percent change in weight	0.274**	0.403*	0.351**	1.514**	0.091*
Baseline waist	0.294	0.409	0.211	−0.585	0.013
Age	−0.025	0.520	0.016	0.301	−0.021
White race/ethnicity	−2.022	5.980	−0.964	1.428	−0.420
Dietary intervention	0.0033	−1.380	−0.597	−5.874*	−0.167
Step-test heart rate	−0.036	0.071	0.058	−0.053	−0.008
Waist-to-height ratio	−24.329	−72.124	−24.980	95.266	4.740
	Models Predicting 24-Month Biomarker Values (n=383)				
	Insulin (R^2=0.52)	Cholesterol (R^2=0.39)	Glucose (R^2=0.31)	TG (R^2=0.56)	CRP (R^2=0.07)
Baseline level of biomarker	0.770**	0.505**	0.525**	1.150**	0.430*
Baseline weight	0.073	−0.300	0.104	0.673	−0.060
Percent change in weight	0.399**	0.544*	0.406**	1.788**	0.064
Baseline waist	−0.173	0.847	−0.306	−2.147	−0.029
Age	0.067	0.637**	0.064	0.817	−0.098
White race/ethnicity	−0.744	5.592	−1.137	−3.287	−2.545
Dietary intervention	0.264	−2.682	0.423	−6.210	0.917
Step-test heart rate	0.001	0.277	0.069	−0.324	0.872
Waist-to-height ratio	31.76	−127.74	31.81	211.26	0.829

CRP indicates C-reactive protein; TG, triglycerides.
*P<0.01, **P<0.001. Values shown are β coefficients in a regression model for each biomarker during each period.

strongly and inversely associated with follow-up measures in the individual marker. Percent change in weight was also associated with modification of biomarkers at 12 and 24 months, particularly for reductions in triglyceride values. Baseline weight or waist circumference was not associated with change in any of the markers.

To further evaluate the relationship between weight change and changes in cardiometabolic biomarkers, models were stratified at a 10% cut point in weight loss percentage and evaluated at the 12 and 24 month follow-up points (Table 3). At 12 months, 167 women had lost at least 10% of initial body weight (48.4% of those randomized to the intervention arms and 13.9% of those in the usual care arm; data not shown). In these women, CRP was reduced from 4.0 to 2.6 mg/L. Waist-to-height ratio (WHtR), total cholesterol, and low-density lipoprotein–cholesterol (LDL-C) were reduced regardless of weight loss percentage (Table 3). Most lipids (except triglycerides) did not show significant interactions between degree of weight loss and degree of lipid change over time (data not shown). All other cardiometabolic risk factors shown in Table 3 had significant interactions between degree of weight loss and time (P<0.01 for each).

At 24 months, 130 women had lost ≥10% of their initial body weight (28.8% of those in the intervention groups and 17.5% of those randomized to usual care; data not shown). Reductions in triglycerides, glucose, insulin, and HOMA-IR were only evident in women who lost ≥10% body weight at follow-up. Cardiopulmonary fitness (based on the 3-minute step test) also improved in study participants. Interestingly, this effect was independent of the degree of weight loss only at 12 months (Table 3). After 24 months, cardiopulmonary fitness significantly improved only in women whose weight loss was ≥10%, whereas it was significantly reduced in those who did not lose 10% of their initial weight compared with baseline values (Table 3).

To evaluate the clinical relevance of the change in cardiometabolic risk factors, an analysis was completed to assess overall change in metabolic markers over time as well as change within clinical cut-point substrata. Of note, all the biomarkers showed significant interactions between risk level and time (P<0.001 for each), and there was a significant interaction between weight loss and time. Generally, the higher the baseline biomarker values, the greater was the reduction with weight loss, as was shown for CRP, choles-

Table 3. Evaluation of Cardiometabolic Risk Factors, Stratified at 10% Weight Loss After 12 and 24 Months Separately

	Lost 10% of Weight After 12 Months (n=167)		Did Not Lose 10% of Weight After 12 Months (n=240)		Lost 10% of Weight After 24 Months (n=130)		Did Not Lose 10% of Weight After 24 Months (n=253)	
	Baseline	12 Months	Baseline	12 Months	Baseline	24 Months	Baseline	24 Months
Weight (kg), mean (SD)	93.2 (11.3)	77.3 (10.7)**	91.0 (10.3)	88.3 (11.2)**	93.3 (10.3)	77.3 (10.1)**	91.0 (10.9)	89.7 (11.9)*
Waist (cm), mean (SD)	109.1 (9.5)	93.8 (8.5)**	107.8 (9.4)	102.7 (9.5)**	109.0 (9.2)	94.8 (8.9)**	107.8 (9.5)	104.2 (9.8)**
Waist/height ratio	0.66 (0.06)	0.58 (0.05)**	0.66 (0.06)	0.63 (0.06)**	0.66 (0.06)	0.57 (0.06)**	0.66 (0.06)	0.63 (0.06)**
BMI, mean (SD)	33.9 (3.4)	28.2 (3.4)**	33.7 (3.4)	32.7 (3.8)**	34.0 (3.3)	28.2 (3.4)**	33.6 (3.4)	33.2 (4.0)*
CRP (mg/L), mean (SD)	4.0 (3.5)	2.6 (5.6)**	4.3 (3.9)	4.0 (5.7)**	3.9 (3.1)	2.2 (2.8)**	4.2 (3.9)	5.0 (11.3)
TG (mg/dL), mean (SD)	107 (48)	94 (39)**	113 (64)	114 (63)	104 (45)	92 (33)**	114 (56)	124 (61)**
Glucose (mg/dL), mean (SD)	94 (11)	93 (24)	94 (11)	96 (13)*	93 (10)	89 (11)**	94 (11)	96 (14)
Insulin (μU/mL), mean (SD)	16.9 (9.1)	12.9 (10.0)**	18.2 (8.7)	17.5 (9.2)	16.3 (8.1)	13.3 (6.2)**	18.1 (8.6)	21.1 (12.2)**
HOMA-IR, % insulin resistant†	62%	35%**	68%	65%	61%	39%**	67%	78%**
Step-test heart rate/ 30 s, mean (SD)	54 (10)	46 (9)**	54 (9)	50 (9)**	54 (9)	46 (8)**	54 (10)	50 (9)**
Step test poor to fair, %	68.5	30.7**	70.2	58.4**	68.5	36.8**	46.1	87.1**
Step test good to outstanding, %	31.5	69.3**	29.8	41.6**	31.5	63.8**	53.9	12.9**

BMI indicates body mass index; CRP, C-reactive protein; HOMA-IR, homeostasis model assessment of insulin resistance; SD, standard deviation; TG, triglycerides.
*$P<0.01$ for change between baseline and follow-up in log-transformed analysis.
**$P<0.001$ for change between baseline and follow-up in log-transformed analysis.
†Homeostasis model for insulin resistance. Insulin sensitive is <3; insulin resistant is ≥3.

terol, LDL-C, triglycerides, glucose, and insulin (Table 4). Overall, a significant number of women entered the weight loss intervention with elevated cardiometabolic risk biomarkers including 200 with CRP >3.0 mg/L, 178 with total cholesterol >200 mg/dL, 139 with elevated LDL, and 252 with low HDL. In a sensitivity analysis that excluded women (n=10) who began a lipid-lowering agent during the trial, results of lipid changes were essentially unchanged (data not shown). At baseline, all women had a WHtR above the recommended cutoff point of 0.5; mean waist circumference was significantly reduced after 12 and 24 months. Elevated fasting insulin (n=227) and glucose (n=96) were also common. Regression to the mean was observed in some of the strata. In sensitivity analyses limited to postmenopausal women, outcomes were similar to those in the entire cohort.

Discussion

In this study of overweight women, participants in a longer term weight loss program lost an average of 7% of baseline body weight at the 2-year follow-up. Weight loss resulted in improvement in numerous cardiometabolic risk factors, including biochemical values and a functional test of cardiopulmonary fitness. Importantly, the improvements in most risk factors were evident at both 12 and 24 months despite modest recidivism in weight loss over time. These results are supported by several shorter-term studies, including an 8-week study by Te Morenga et al in 83 adults, in which weight loss ranged from 3.3 to 4.5 kg and resulted in significant reductions in LDL-C, triglycerides, and glucose.[8] Similarly, a weight loss intervention by Muzio et al resulted in significant reductions in weight, waist circumference, triglycerides, and LDL-C after 5 months.[11] Short-term studies have also demonstrated a reduction in CRP,[25] but seldom to the degree necessary to reduce clinical risk as observed in this trial. In a 12-week weight loss study by Clifton et al in 79 overweight/obese adult women, significant weight loss also was demonstrated, but importantly, this is 1 of only a few trials that reassessed the intervention efficacy longer term.[10] As with the present study, long-term improvements in glucose, insulin, CRP, and LDL-C were demonstrated.[10]

There have been only a limited number of longer-term studies, but a few have evaluated changes in cardiometabolic parameters over time in relation to weight loss. Four-year data from the LookAHEAD trial, a study performed in individuals with type 2 diabetes, support our results and show that a lifestyle intervention aimed at weight reduction results in significant reductions in triglycerides and LDL-C.[26] In 1 of the larger samples studied, Foster et al showed an 11-kg average

Table 4. Cardiometabolic Risk Factors at Baseline and After 12 and 24 Months of Weight Loss Study Participation, Overall and Stratified by Clinical Risk/Cut Points

Risk Factor	Baseline (n=417)	n*	12 Months (n=407)	n*	24 Months (n=383)
CRP (mg/L), mean (SD)	4.2 (3.7)	407	3.4 (5.7)**	383	4.1 (9.4)**
CRP <1 (low risk)	0.6 (0.2)	38	0.8 (0.6)**	35	1.0 (0.7)**
CRP 1 to 2.99 (medium risk)	1.9 (0.6)	169	1.9 (3.9)	164	3.1 (12.8)
CRP ≥3 (high risk)	6.6 (3.9)	200	5.1 (6.8)**	184	5.4 (6.2)**
Total cholesterol (mg/dL), mean (SD)	196 (36)	406	189 (36)	383	184 (37)**
<200	171 (21)	228	172 (28)	215	168 (27)
≥200	229 (21)	178	211 (34)**	168	204 (37)**
LDL-cholesterol (mg/dL), mean (SD)	117 (33)	405	111 (34)*	382	113 (37)
<130	98 (20)	266	99 (27)	255	104 (33)
≥130	154 (17)	139	133 (35)**	127	132 (38)**
HDL-cholesterol (mg/dL), mean (SD)	57 (16)	405	57 (16)	383	53 (15)*
<60	47 (8)	252	52 (13)**	239	47 (10)
≥60	73 (12)	153	66 (15)**	144	63 (17)**
Non-HDL-cholesterol (mg/dL), mean (SD)	139 (36)	405	132 (35)*	383	131 (38)*
<160	122 (24)	294	121 (28)	280	120 (30)
≥160	185 (19)	111	162 (38)*	103	159 (42)*
Triglycerides (mg/dL), mean (SD)	90 (26)	406	106 (55)	383	117 (93)
<150	90 (26)	337	93 (34)	317	100 (43)**
≥150	204 (69)	69	168 (89)**	66	195 (186)*
Glucose (mg/dL), mean (SD)	94 (11)	406	95 (18)	383	94 (13)
<100	89 (7)	310	91 (9)	293	91 (10)
≥100	109 (9)	96	107 (32)	90	101 (18)**
Insulin (μU/mL), mean (SD)	17.8 (8.9)	407	15.6 (9.8)**	383	18.5 (11.2)
<15	11.1 (2.7)	180	11.0 (4.5)	174	13.4 (5.5)**
≥15	23.1 (8.5)	227	19.3 (11.2)**	209	22.7 (12.8)
HOMA-IR‡	4.21 (2.53)	405	3.72 (2.58)**	383	4.37 (3.10)
<3	2.26 (0.54)	138	2.39 (1.11)	135	2.95 (1.38)**
≥3	5.24 (2.57)	267	4.41 (2.84)**	248	5.15 (3.49)
Waist (cm), mean (SD)	108.3 (9.5)	409	99.0 (10.1)**	392	101.1 (10.7)**
<88	86.7 (1.2)	4	86.0 (11.3)	4	82.9 (6.5)
≥88	108.5 (9.3)	405	99.2 (10.0)**	388	101.3 (10.5)**
Waist/height ratio, mean (SD)					
<0.5	N/A				
≥0.5	0.66 (0.06)	409	0.60 (0.06)**	392	0.61 (0.07)**

CRP, C-reactive protein; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; SD, standard deviation;
*P<0.01, compared with baseline in log-transformed analysis.
**P<0.001, compared with baseline in log-transformed analysis.
†Sample size represents the number within stratum at baseline and after 12 or 24 months and varies based on completion of 12- or 24-month clinic activities.
‡Homeostasis model for insulin resistance. Insulin sensitive is <3; insulin resistant is ≥3.

weight loss at year 1 (n=307; 68% female) and 7-kg loss at year 2 (n=113),[27] weight loss effects similar to what was achieved in our sample. Consistent with our findings, triglycerides improved at year 1 and were not significantly different from baseline at year 2 in either study. Their results suggested no significant reduction in LDL-C at 24 months,[27] though participants in our trial who had elevated baseline values demonstrated significant reductions in LDL-C even

after 24 months. In a study of 176 overweight/obese adults of whom 87% were female, Burke et al showed significant improvements in total cholesterol and the LDL:HDL ratio as well as HOMA-IR, a measure of insulin resistance, after 12 months of intervention, changes that were generally sustained at the 6-month postintervention follow-up.[28] These results, taken into consideration with our results, suggest that efforts to favorably modulate cardiometabolic risk factors through modest weight loss in numerous short-term trials generally translate to longer-term follow-up, even with modest weight regain between 12 and 24 months.

Improvements in several CVD risk factors were demonstrated in response to participation in this weight loss study. WHtR is an adiposity index that more accurately predicts cardiometabolic risk than BMI or waist circumference.[23,29] In this study, WHtR was reduced regardless of the degree of weight lost, although this effect was more pronounced in women who lost ≥10% of their initial body weight, as evidenced by the significant interaction between WHtR and weight. Recent evidence also indicates that non-HDL-cholesterol more accurately predicts risk of coronary heart disease than LDL-C, as it encompasses all cholesterol-containing atherogenic particles including LDL-C and very-low-density lipoprotein–cholesterol.[30] On average, women with elevated baseline non-HDL-cholesterol (≥160 mg/dL) demonstrated reductions to within a normal range after 24 months, and non-HDL cholesterol values were reduced at 12 and 24 months, regardless of the degree of weight loss. The literature regarding lifestyle interventions for weight loss and non-HDL-cholesterol response is extremely limited, although our findings suggest that any amount of weight loss may reduce non-HDL levels.

Previous work has demonstrated that reductions in insulin resistance are observed with increases in physical activity, independent of weight loss.[31] Other intervention studies for weight reduction agreed that exercise is a necessary component, in addition to diet modification, to reduce insulin resistance.[32] In this study, diet was the major lifestyle modification addressed, but regular physical activity was also promoted through counseling. In response, insulin levels and, perhaps more importantly, HOMA-IR values were significantly reduced at 12 months, but only in women who demonstrated weight loss ≥10% of their initial body weight. We cannot ascertain if this effect was due solely to changes in diet and/or physical activity.

This study also had the benefit of evaluating cardiopulmonary fitness, an indicator of health also known to improve with physical activity.[33] Performance improved over time regardless of percent weight loss but was not associated with cardiometabolic factors. These results suggest that efforts to expand outcome measures in weight loss studies targeting improved cardiometabolic risk should consider biochemical biomarkers as well as functional measures. Improvements in cardiopulmonary fitness have been reported in other weight loss studies,[32,34] although not consistently.[35]

Although control for baseline values of the respective outcome (ie, weight, biomarker) when conducting regression analysis is sometimes applied, estimation of the predictive nature of the baseline value is seldom evaluated.[36] Our results suggest that 1 important predictor of change in cardiometabolic biomarkers is the baseline level of the individual biomarker. These data suggest that lifestyle interventions targeting weight loss are effective for improving cardiometabolic risk in individuals who present with unfavorable measures. Our data suggest that these measures show significant and sustained improvement if any degree of weight loss is achieved and maintained.

Limitations to this study include a lack of assessment of lipoprotein particle size, known to be associated with cardiovascular risk[37] and responsive to dietary intervention.[9] Further, we did not conduct hemodynamic measures such as blood pressure during the 3-minute step test. These measures likely would have provided more robust data regarding cardiopulmonary fitness.[33] However, cardiopulmonary fitness was not a primary end point of this study, and although less accurate than measuring maximal oxygen uptake (VO_{2max}) and hemodynamics during test administration, the 3-minute step test has high reliability, is sensitive to change, and has been used broadly to assess change in cardiopulmonary fitness in clinical trials.[24] We did not collect specific information on diet or physical activity that can influence these biomarkers; however, it is apparent that women were generally in negative energy balance given the substantial weight loss demonstrated by so many study participants. It is well recognized that negative energy balance can modulate many of these targeted risk factors whether that occurs through dietary intervention or in combination with physical activity.[11,25,26,30,35,36,38,39] Last, the results of this study may not represent effects of weight loss on cardiometabolic risk factors in a clinical population under direct care, including medications, to treat their disease.

Strengths of the trial include the 24-month intervention and follow-up period in a relatively large sample of women with robust and repeated measures of cardiometabolic risk factors. The sample size and variance in weight loss also afforded an opportunity to ascertain differences in risk factors over time in women who were more (≥10% body weight loss) versus less (<10% body weight loss) responsive to the weight loss interventions.

In conclusion, participation in a weight loss study resulted in significant reductions in body weight, BMI, and waist circumference after 12 and 24 months. This weight loss was associated with significant improvements in several of the

cardiometabolic risk factors that are commonly assessed in the clinical setting. Moreover, weight loss of ≥10% after 12 months produced significant reductions in these risk factors, often lowering the risk factor from a category of high risk to that of medium or low risk (ie, CRP and insulin). These data also show that baseline cardiometabolic risk factors (cholesterol, fasting glucose, insulin, triglycerides, and CRP) have significant predictive value in determining favorable risk reduction response to weight loss, suggesting that these risk factors could be used to identify women more likely to respond favorably to weight loss interventions.

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Disclosures

None.

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