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Weight Cycling and High-density Lipoprotein Cholesterol in Women: Evidence of an Adverse Effect

A Report from the NHLBI-sponsored WISE Study

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OBJECTIVES We undertook an analysis of weight cycling, coronary risk factors and angiographic coronary artery disease (CAD) in women.

BACKGROUND The effect of weight cycling on cardiovascular mortality and morbidity is controversial, and the impact of weight cycling on cardiovascular risk factors is unclear.

METHODS This is a cross-sectional population study of 485 women with coronary risk factors undergoing coronary angiography for evaluation of suspected myocardial ischemia enrolled in the Women's Ischemia Syndrome Evaluation (WISE). Reported lifetime weight cycling—defined as voluntary weight loss of at least 10 lbs at least 3 times—coronary risk factors including core laboratory determined blood lipoproteins and CAD, as determined by a core angiographic laboratory, are the main outcome measures.

RESULTS Overall, 27% of women reported weight cycling—19% cycled 10 to 19 lbs, 6% cycled 20 to 49 lbs, and 2% cycled 50+ lbs. Reported weight cycling was associated with 7% lower high-density lipoprotein cholesterol (HDL-C) levels in women ($p = 0.01$). The HDL-C effect was directly related to the amount of weight cycled with women who lost ≥50 lbs/cycle having HDL-C levels 27% lower than noncyclers ($p = 0.0025$). This finding was independent of other HDL-C modulators, including estrogen status, physical activity level, alcohol intake, body mass index, diabetes, beta-blocker use, cigarette smoking and race. Weight cycling was not associated with an increased prevalence of CAD in this population.

CONCLUSIONS Weight cycling is associated with lower HDL-C in women of a magnitude that is known to be associated with an increased risk of cardiac events as demonstrated in prior clinical trials. (J Am Coll Cardiol 2000;36:1565–71) © 2000 by the American College of Cardiology

The effect of weight cycling (repeated weight loss and weight gain) on cardiovascular mortality and morbidity is controversial. Previous studies have shown that while weight loss has a beneficial effect on cardiovascular risk factors in obese patients, especially those with comorbidities (1,2), weight cycling may confer an elevated risk of death from cardiovascular disease (3–6). In 1994, the National Task Force on the Prevention and Treatment of Obesity concluded, "Although conclusive data on the long-term effects of weight cycling are lacking, non-obese individuals should attempt to maintain a stable weight" (7). Given that 40% of adult women report attempts to lose weight (8), there is a compelling need for investigation in this area.

Investigation into biologically plausible mechanisms, whereby weight cycling might elevate cardiovascular risk, is limited. Studies evaluating weight loss and regain in animals have been inconsistent (9). Previous studies performed on obese/overweight women and men have failed to demonstrate any adverse relationships between weight cycling and coronary risk factors (10,11). Finally, much of the previous work has not distinguished intentional from unintentional weight loss (7).

We undertook an analysis of weight cycling, coronary risk factors and angiographic coronary artery disease (CAD) in women enrolled in the Women's Ischemia Syndrome Evaluation (WISE). We hypothesized that weight cycling would be associated with an adverse effect on coronary risk factors, thereby potentially promoting the development of CAD.

METHODS

The WISE study is a National Heart, Lung and Blood Institute (NHLBI) sponsored four-center study that aims to

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Abbreviations and Acronyms

BMI = body mass index
CAD = coronary artery disease
HDL-C = high-density lipoprotein cholesterol
HRT = hormone replacement therapy
NHLBI = National Heart, Lung and Blood Institute
PEPI-Q = Postmenopausal Estrogen/Progesterone Intervention Activity Questionnaire
TC = total plasma cholesterol
WISE = Women's Ischemia Syndrome Evaluation

improve the diagnostic reliability of cardiovascular testing in the evaluation of ischemic heart disease in women. Each center obtained appropriate institutional review board approval and participant consent before the initiation of testing. Women with chest pain symptoms or suspected ischemia undergo an initial evaluation that includes the collection of demographic, medical history, psychosocial and symptom data as well as blood sampling. Subjects also undergo a physical examination that includes height, weight and waist-hip ratio determination, followed by quantitative coronary angiography. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters; a BMI of >30 was defined as obese (12). Determination of waist-hip ratio involved measurement of the waist at the natural waistline and the hip at the widest part, across the buttocks. Blood pressure was measured twice using a standard protocol. An average of the two measurements was used for data analysis. The complete study design and methodology of the WISE study are described elsewhere (13).

Definition of weight cycling. During the baseline evaluation each woman was asked about the number of times in her life that she had intentionally lost a specified number of lbs through dieting, exercise, a formal weight control program or on her own. Pregnancy and childbirth were not included. Ranges of weight were indicated rather than actual weight loss. Women were asked to select from five weight-loss ranges, beginning with 10 to 19 lbs and ending with 100 or more lbs. The number of times that the women had lost the weight ranged from never to more than 10 times. For the purpose of these analyses, weight cycling was defined a priori as weight loss of at least 10 lbs at least 3 times.

Lipoprotein analyses. Lipoprotein determinations were performed at a lipid core laboratory enrolled in the Centers for Disease Control and prevention lipid standardization program previously used in multiple NHLBI-sponsored lipid-lowering intervention trials. Total plasma cholesterol (TC), triglycerides and high-density lipoprotein cholesterol (HDL-C) were determined by enzymatic assay, and low-density lipoprotein cholesterol was calculated using the Friedewald formula, as previously published (14). The coefficients of variation for TC, HDL-C and triglycerides were 1.80%, 1.23% and 3.93%, respectively.

Measures of physical activity and functional capacity. A version of the Postmenopausal Estrogen/Progesterone Intervention Activity Questionnaire (PEPI-Q) (15) was used to assess physical activity. The PEPI-Q is a brief questionnaire that covers three areas of physical activity: activity at work, home and during leisure time. The total PEPI-Q score was calculated, and then the score was weighted to account for "Not Applicable" responses for women not employed outside the home. The weighting involved substituting the average value on completed questions for this item. The scores ranged from 1.5 to 12, with a higher score indicating greater activity. The Duke Activity Status Index (16) was used to assess functional capacity. This 12-item scale measures the ability to perform common daily activities. Again, a higher score is indicative of greater functional capacity.

Risk factors. The risk factors examined were from the National Cholesterol Education Program Adult Treatment Panel II (17) and included age 55 years or older or menopause without current hormone replacement therapy (HRT), positive family history for CAD (CAD in male first degree relative <55 years old or a female first degree relative <65 years old), current cigarette smoking, hypertension (history of hypertension or blood pressure >140 mm Hg systolic or >90 mm Hg diastolic), HDL-C <35 mg/dl and a history of diabetes mellitus.

Measurement of quantitative angiography. Coronary angiograms were analyzed by a core laboratory used in previous multicenter trials with angiographic outcomes. Measurements included quantitative assessment as to the presence, severity and complexity of epicardial coronary artery stenoses, using previously published methods (18).

Statistical analysis. Comparisons between reported weight cyclers and noncyclers were performed by the Wilcoxon rank-sum test for continuous measures and by the chi-square test for discrete measures. Probability values of ≤ 0.05 were considered statistically significant. The relationship between obesity (BMI > 30) and reported weight cycling with HDL-C levels was assessed using a general linear model. This kind of modeling was also used in examining the relationship between amount of weight lost during each cycle and HDL-C. Stepwise regression analysis was used to model HDL-C as a function of weight cycling and other coronary risk factors including race, age, BMI, waist-hip ratio, physical activity, functional capacity, diabetes, menopausal status, current HRT, alcohol and beta-blocker agent use. These variables were chosen for entry into the model based upon univariate and multivariate associations as well as literature review of relevant, confounding variables. Criteria for entry into the model was $p = 0.15$. Analyses were performed using SAS software release 6.12.

RESULTS

Reported weight cycling by participant characteristics is shown in Table 1. One hundred thirty (27%) women

Table 1. Reported Weight Cycling by Participant Characteristics

Characteristic	n	Weight Cycle %	Do Not Weight Cycle %	p Value
Race				
White	395	30	70	0.003
Other	90	14	86	
Education				
<High school	101	19	81	0.04
High school	208	27	73	
>High school	175	31	69	
BMI*>30	191	37	63	0.001
BMI ≤30	290	20	80	
Postmenopausal				
Yes	366	26	74	0.67
No	117	28	72	
HRT currently (postmenopausal)				
Yes	152	28	72	0.75
No	203	26	74	
Diabetes†				
Yes	93	30	70	0.42
No	392	26	74	
CAD (≥50% ≥1 coronary artery)				
Yes	186	24	76	0.34
No	244	28	72	

*Body mass index calculated as described in Methods; †history of diabetes treated with insulin and/or oral medication.
BMI = body mass index; CAD = coronary artery disease; HRT = hormone replacement therapy; n = number of women; % = % in category.

reported a history of weight cycling; 19% cycled 10 to 19 lbs, 6% cycled 20 to 49 lbs, and 2% cycled 50+ lbs. Overall, 426 (88%) of the women had at least one National Cholesterol Education Program Adult Treatment Panel II risk factor, and 334 (69%) had multiple (two or more) risk factors.

Women who reported weight cycling were younger (Table 2), more often white and better educated compared with noncyclers (Table 1). However, there was no difference between reported cyclers and noncyclers in menopausal status, the proportion currently using HRT, diabetes or the prevalence of CAD (Table 1).

Comparison of coronary risk factors and angiographic CAD among women reporting weight cycling compared with those reporting no weight cycling is shown in Table 2. Notably, women reporting weight cycling had significantly lower HDL-C levels (7%) ($p = 0.01$) and higher (8%) TC/HDL-C ($p = 0.03$) than noncyclers. They also had a higher BMI at study entry, higher levels of physical activity and higher functional capacity. There was no difference between cyclers and noncyclers for the usual cardiac risk factors such as blood pressure, fasting blood sugar or waist-hip ratio.

Table 2. Coronary Risk Factors by Reported Weight Cycling

Risk Factor	n	Weight Cycle (n = 130)	n	No Weight Cycle (n = 355)	p Value
Age (yrs) (±SD)	130	55.8 ± 10.8	355	59.7 ± 11.8	0.001
Systolic blood pressure (mm Hg) (±SD)	130	134 ± 18	355	138 ± 22	0.16
Diastolic blood pressure (mm Hg) (±SD)	130	77 ± 11	355	76 ± 11	0.30
Fasting Blood Sugar (mg/dl) (±SD)	76	126 ± 64	231	118 ± 58	0.27
TC (mg/dl) (±SD)	124	201 ± 44	342	203 ± 46	0.75
Triglycerides (mg/dl) (±SD)	122	163 ± 153	341	159 ± 97	0.78
HDL-C (mg/dl) (±SD)	120	52 ± 12	338	56 ± 14	0.01
LDL-C (mg/dl) (±SD)	118	120 ± 42	336	115 ± 40	0.28
TC/HDL-C (±SD)	120	4.1 ± 1.4	338	3.8 ± 1.1	0.03
Weight (lbs) (±SD)	130	182 ± 35	351	163 ± 36	0.0001
BMI* (±SD)	130	32 ± 7	351	29 ± 6	0.0001
Waist-hip ratio (±SD)	112	0.87 ± 0.11	351	0.87 ± 0.11	0.57
Alcohol intake (drinks/week) (±SD)	129	0.60 ± 3.3	355	0.67 ± 3.9	0.32
Physical activity (±SD)	130	7.7 ± 1.7	355	7.1 ± 2.0	0.0008
Functional capacity (±SD)	130	20.7 ± 12.8	355	18.1 ± 13.2	0.02

*BMI = body mass index calculated as described in Methods.
HDL-C = high-density lipoprotein cholesterol; lbs = pounds; LDL-C = low-density lipoprotein cholesterol; SD = standard deviation; TC = total cholesterol.

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Table 3. Significant Independent Predictors of HDL-C (mg/dl) (Linear Regression Model)

Variable	Parameter Estimate (± SE)†	p Value
Weight cycling (yes vs. no)	−3.43 (± 1.51)	0.02
BMI	−0.38 (± 0.11)	0.0001
Current smoker (yes vs. no)	−6.49 (± 1.66)	0.0001
Current HRT (yes vs. no)	3.61 (± 1.33)	0.001
Diabetes* (yes vs. no)	−4.39 (± 1.75)	0.008
Waist-hip ratio	−13.75 (± 6.15)	0.02
Intercept	82.45 (± 6.03)	—

*History of diabetes treated with insulin and/or oral medications; †SE = standard error. Race, age, activity, alcohol consumption, functional capacity and use of beta-blockers were considered but were not significant independent explanatory variables.

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; HRT = hormone replacement therapy; SE = standard error.

Next, we evaluated whether reported weight cycling independently contributed to the lower observed HDL-C levels. Weight cycling was shown to be an independent, significant predictor of HDL-C (Table 3), taking into account age, race, BMI, current smoking, current HRT use, diabetes, waist-hip ratio, alcohol consumption, physical activity, functional capacity, menopausal status and use of beta-blockers. When we controlled for known modulators of HDL-C, such as BMI, current HRT and cigarette smoking, the same predictors were found with similar p values.

Since elevated BMI was one of the strongest and most prevalent determinants of reduced HDL-C, we stratified women into four groups according to the presence or absence of obesity (BMI > 30) and weight cycling (Table 4). Both weight cycling and obesity were significant factors in the model. The mean BMI of the obese women (both cyclers and noncyclers) was 36, while the non-obese had a mean BMI of 27 (cyclers) and of 25 (noncyclers). Women who were both obese and reported weight cycling had the lowest HDL-C levels, while women with neither characteristic had the highest (p = 0.001).

We examined different thresholds of weight cycling to ascertain if there is a "dose-effect" relationship between reported weight cycling and lower HDL-C. Similar magnitudes of lower HDL-C were observed in the groups of women who reported weight cycling at different thresholds, greater or equal to 3, 6 or 10 times compared with those with fewer than 3, 6 or 10 cycles, respectively. With the threshold of ≥10 times (n = 41), there was a trend toward a lower HDL-C compared with those who cycled <10 times: 51.6 mg/dl ± 11.7 versus 55.0 mg/dl ± 13.6, respectively (p = 0.14). We also looked at women who reported cycling 3 or more times and lost 10 to 19 lbs, 20 to 49 lbs or ≥50 lbs with each cycle. Lower HDL-C levels were observed with increasing amounts of weight cycled (Fig. 1). There was a trend to increasing BMI with each category of weight loss, and adjustment of the HDL-C levels for BMI did not substantially affect the relationship. Repeat analysis of all the demographic, risk factor and coronary angiographic variables using a lower threshold for obesity (BMI > 27) demonstrated similar results.

Table 4. HDL-C Levels (mg/dl) by Presence or Absence of Obesity/Weight Cycling*

Obese (BMI >30)	Weight Cycling	
	Yes	No
Yes	(n = 65) 49.7 (± 12.2) mg/dl	(n = 116) 53.6 (± 11.3) mg/dl
No	(n = 55) 54.1 (± 11.1) mg/dl	(n = 218) 56.9 (± 14.9) mg/dl

*p = 0.001, both weight cycling and obesity were significant factors in the model. BMI = body mass index; HDL-C = high-density lipoprotein cholesterol.

DISCUSSION

Effect of weight cycling. This study's findings demonstrate that reported weight cycling is associated with lower HDL-C levels in women with multiple risk factors being evaluated for suspected myocardial ischemia. Our findings of 3 mg/dl to 5 mg/dl lower HDL-C levels in women with reported weight cycling as compared with noncyclers and as much as a 15 mg/dl lower value for women reporting large (≥50 lbs) weight cycles could have widespread clinical significance. The 7% difference in HDL-C between cyclers and noncyclers is of a similar magnitude as that recently shown in men to impact major coronary events in the Veterans Affairs Cooperative Studies Program High-Density Lipoprotein Cholesterol Intervention Trial (19). After 5 years of follow-up a 6% increase in HDL-C levels using gemfibrozil resulted in a 22% reduction in major coronary events. Similar results were found in the earlier Helsinki Heart Study (20).

The adverse effect of weight cycling on HDL-C levels appears to be independent from other known modulators of HDL-C, specifically BMI, (21,22) abdominal adiposity, cigarette smoking, physical activity level, alcohol intake, HRT (23), diabetes (24) and race. The biologic plausibility of these findings is further supported by a "dose-response" effect showing that the greater magnitudes of reported weight cycled are associated with significantly lower HDL-C levels.

Coronary risk factors. These results document an association between a measure of weight cycling and a significant coronary risk factor, HDL-C. While controversy still exists regarding how best to define weight cycling, large epidemiologic studies using a variety of measures (3–6,25) have predominantly indicated an adverse effect for all-cause and cardiovascular mortality. Notably, we did not find a significant association between reported weight cycling and angiographic CAD, suggesting that the potential link between weight cycling and cardiovascular mortality may be non-atherogenic. Alternatively, there may be a lag time between decreases in HDL-C and their effect on the development of CAD since our weight cyclers were younger compared with noncyclers. We are unable to evaluate this with our current data. The relatively low prevalence of significant CAD in

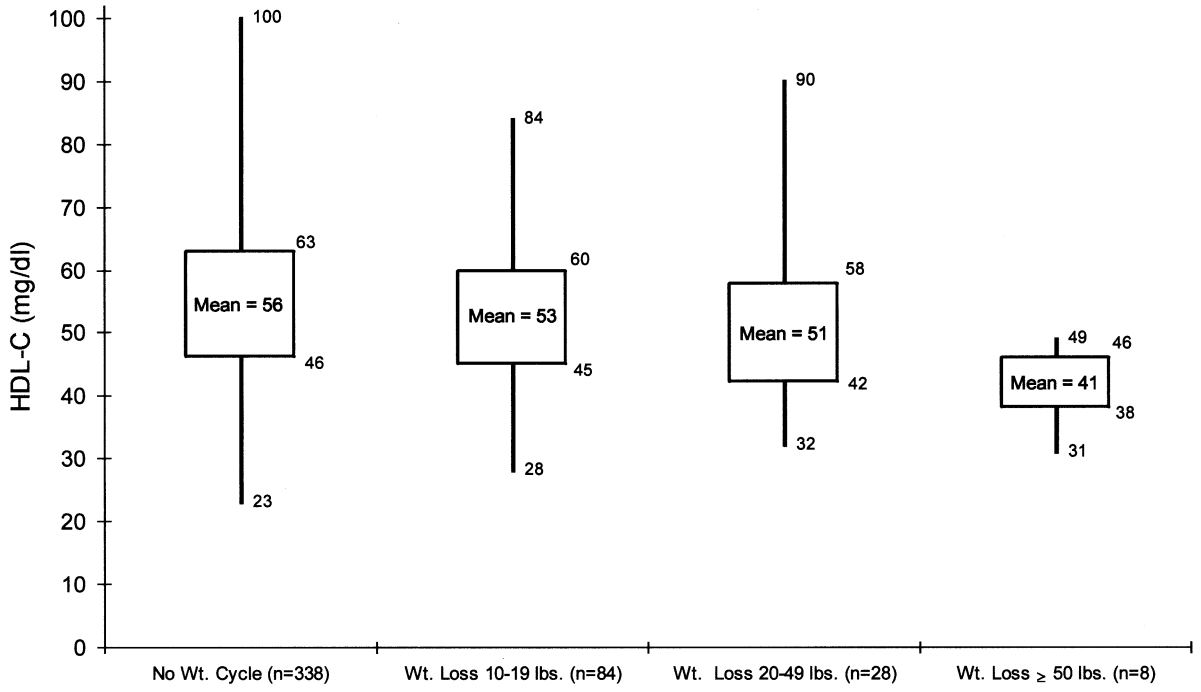

Figure 1. Box plots of HDL-C levels (mg/dl) by magnitude of weight cycled at least 3 times. Extreme values are at the ends; quartile values are on the corners of the box. p = 0.0025 (general linear model). HDL-C = high-density lipoprotein cholesterol.

our women may also have limited our ability to detect a relationship between weight cycling and CAD. Previous work analyzing various measures of weight cycling and coronary risk factors has been mainly negative for significant associations (10,11). Human studies have predominantly studied obese, but otherwise healthy, subjects attempting weight loss and not high risk women with multiple coronary risk factors undergoing evaluation of suspected CAD, as in this study population.

Current study procedures. The current study data collection and quantitation procedures represent an improvement compared with prior related study methods. Women's Ischemia Syndrome Evaluation used study coordinator-directed historical questionnaire data collection, rather than mail-in self-report, and women were asked specifically about intentional weight loss. Lipoprotein determinations were performed in batch analyses by a Centers for Disease Control standardized core lab, with known excellent coefficients of variation. We also measured potentially confounding variables not assessed previously in weight cycling studies, such as waist-hip ratio, physical activity, alcohol intake, menopausal status and hormone replacement use. Not measuring and adjusting for these variables may have confounded a relationship of HDL-C and weight cycling in earlier studies. For example, our women reporting weight cycling were significantly more physically active compared with non-weight cyclers, which, as a beneficial moderating variable of HDL-C, may have masked an adverse HDL-C effect in prior studies.

Mechanisms. Possible biologic mechanisms linking weight cycling and lower HDL-C levels in women are speculative. Intentional weight loss typically results from caloric deprivation, shifting basal metabolism to a state of energy conservation and catabolism of endogenous energy stores (26). Metabolic studies have demonstrated that short-term hypocaloric weight loss without change in physical activity results in a minor HDL-C decrease (0.27 mg/dl), which shifts to an increase during weight stabilization (0.35 mg/dl) (27). This change appears to be driven by the sympathetic nervous system-mediated insulin and thyroid hormone level reductions, which conserve energy by reducing thermogenesis (26). Weight cycling may reduce HDL-C levels by contributing to the dysmetabolic syndrome of insulin resistance/impaired glucose tolerance, abdominal adiposity and hypertension associated with CAD (28). This concept is consistent with our findings that weight cycling is an independent predictor of HDL-C, even after adjustment for diabetes in the multivariate model. The ultimate metabolic pathways responsible for determining a net HDL-C effect of repeated weight loss and weight gain are likely complex and individually mediated. Further work is needed to evaluate the possible metabolic pathways linking weight cycling and HDL-C.

Study limitations. The current study results are limited by the cross-sectional design, which precludes inference regarding causality between reported weight cycling and HDL-C. Additionally, we are unable to control for unmeasured variables or draw conclusions regarding a pathophysiological sequence of associations. We did not collect

information on how recently the last weight cycling occurred or about the use of diet pills/sympathetic nervous system stimulants as aids to weight loss. Use of self-reported weight cycling can also be viewed as a limitation compared with actual body weight measurement over time. However, there are drawbacks to these methods as well (29). The relevance of our HDL-C findings is reduced by the lack of concurrent adverse coronary angiographic findings. The WISE enrollment is continuing, and these relationships will be examined in the larger population at the end of the study. Alternatively, the lack of concordance with coronary angiography may suggest that HDL-C is a marker of nonatherogenic sympathetic nervous system changes triggered by weight cycling that could increase cardiovascular mortality.

Our study consists of women with chest pain symptoms suspected to be ischemic and referred for coronary angiography; biases inherent in this population (30) may also limit generalizability.

Relevance. Low HDL-C is a particularly potent risk factor for cardiovascular mortality in women. Follow-up of Framingham women showed a clear inverse association between HDL-C and myocardial infarction (31). Evidence from the largest epidemiological studies suggests that, for each 1 mg/dl increase in HDL-C, a 3% decease in coronary heart disease risk in women may occur (32). The recent American Heart Association/American College of Cardiology guide to preventive cardiology in women (33) makes several recommendations for focused risk factor management in women, including more aggressive targets for HDL-C and triglycerides.

Since this study found a relationship between HDL-C levels and reported weight cycling that is independent of BMI, these results may be relevant to all women who weight cycle, including non-obese women. We conclude with the 1994 recommendation of the National Task Force on the Prevention and Treatment of Obesity, "Although conclusive data on the long-term effects of weight cycling are lacking, non-obese individuals should attempt to maintain a stable weight" (7).

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