Published in final edited form as:

J Cardiovasc Nurs. 2010 ; 25(1): 52–60. doi:10.1097/JCN.0b013e3181b7e500.

The Influence of Cardiac Rehabilitation on Inflammation and Metabolic Syndrome in Women with Coronary Heart Disease

Theresa M. Beckie, PhD, Jason W. Beckstead, PhD, and Maureen W. Groer, PhD

University of South Florida, 12901 Bruce B. Downs Blvd, Tampa, Florida, 33612

Abstract

Background—Metabolic syndrome (MetS) and elevated inflammatory markers, both predictors of future cardiovascular events, are more prevalent in women with coronary heart disease (CHD). The influence of cardiac rehabilitation (CR) on MetS and inflammatory biomarkers is not well characterized for women.

Purpose—The purpose of this paper is to examine the effects of a 12-week behaviorally enhanced CR exclusively for women compared to traditional CR on components of the MetS and inflammatory markers in women with CHD.

Methods—The randomized clinical trial employed 2 treatment groups; both receiving a comprehensive 12-week CR program, with 1 group receiving a motivationally enhanced intervention exclusively for women. A subset of 91 women (mean age 61.6 years) from the parent study provided serum samples to examine the effects of CR on high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), and intercellular adhesion molecule-1 (ICAM-1).

Results—Following CR, the total sample of women demonstrated significant reductions in hsCRP ($P=.002$), IL-6 ($P<.001$), TNF- α ($P=.010$), and ICAM-1 ($P=.016$). Women in the gender-tailored CR program, significantly improved all biomarker levels compared to baseline ($P<.05$ for all) while those in the traditional group improved only hsCRP ($P<.05$) and IL-6 ($P<.05$) levels. The combined study group demonstrated improvements in several components of the MetS (triglycerides, waist circumference, and systolic blood pressure) but not others (high-density lipoprotein cholesterol, fasting glucose, and diastolic blood pressure).

Conclusion—Cardiac rehabilitation promotes greater improvements in inflammatory biomarkers than in components of MetS for women with CHD. Improvements in body composition or weight may not be a precondition for the benefits of exercise due to loss of abdominal fat. Examining components of MetS as continuous variables is recommended to prevent lost information inherent in dichotomization.

Keywords

metabolic syndrome; cardiac rehabilitation; inflammation; obesity; c-reactive protein (hsCRP); interleukin-6 (IL-6); intercellular adhesion molecule-1 (ICAM-1); tumor necrosis factor alpha (TNF- α)

Address Correspondence to: Theresa M. Beckie, PhD, College of Nursing, University of South Florida, MDC Box 22, 12901 Bruce B. Downs Blvd., Tampa, Florida, 33612-4766, Telephone: (W) (813) 974-9202, (H) (813) 741-2665, Fax: (813) 974-7903, tbeckie@health.usf.edu.

All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere, in whole or part, in any language except as an abstract.

Coronary heart disease (CHD) remains the leading cause of disability and death in North American women.¹ Heart disease, a chronic multistage inflammatory disease, is influenced by environmental exposures, lifestyle factors, and genetic determinants that are reflected in traditional risk factors, inflammatory biomarkers, and metabolic status. Metabolic syndrome (MetS), a constellation of CHD risk factors, includes atherogenic dyslipidemia (elevated triglycerides and decreased high-density lipoprotein cholesterol (HDL-C)), hypertension, abdominal obesity, hyperglycemia, insulin resistance, and a proinflammatory state.^{2–6} While controversy continues regarding which operational definition is the most appropriate and clinically useful,⁷ it is generally agreed that MetS confers increased risk for CHD⁸ and poor long-term prognosis.^{9–12}

Obesity, a central feature of MetS, is associated with a proinflammatory state⁷ mediated by dysregulated adipose tissue releasing numerous inflammatory cytokines.¹³ Inflammation, a principal driver of MetS, is more prevalent in women,^{14–18} is a stronger predictor of CHD than in men^{8, 19} and women with established CHD are at higher risk for adverse cardiovascular outcomes.²⁰ The most intensively studied inflammatory biomarkers include high-sensitivity c-reactive protein (hsCRP),^{21, 22, 23} an acute phase reactant, interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF- α), both inflammatory cytokines, and intercellular adhesion molecule-1 (ICAM-1),^{21, 24} a marker of endothelial function. C-reactive protein, produced by hepatocytes, is regulated by IL-6 and TNF- α and is found in the endothelium of atherosclerotic plaques, smooth muscle cells, macrophages, and adipocytes.^{25–28} C-reactive protein affects the endothelium by altering the bioavailability of nitric oxide, thus, up-regulating ICAM-1.²⁹

Despite heated debates surrounding the clinical utility of MetS, the cornerstone for improving the components of MetS and inflammation includes weight reduction and exercise training.^{30–33} Evidence supports the anti-inflammatory effects of exercise on biomarkers such as hsCRP in various settings and populations.^{34, 35} Cardiac rehabilitation (CR) programs consisting of prescriptive exercise, health education, and psychological counseling have compelling benefits for improving both physiological and psychosocial outcomes for individuals with CHD.^{36–39} The effects of lifestyle modifications on inflammatory biomarkers have been examined^{40–43} with fewer exploring the effects of CR on MetS and inflammation in CHD participants.^{31, 44–48} Scientific inquiry of the impact of CR on MetS and inflammatory biomarkers in women is particularly meager.^{30, 44} The aim of this paper is to examine the effects of a 12-week behaviorally enhanced CR exclusively for women compared to traditional CR on components of MetS and inflammatory biomarkers in women with CHD.

Methods

Participants

Data analyzed here are from a sub-study of a larger randomized clinical trial that was already underway. Receipt of a supplemental funding award afforded us the opportunity to analyze blood samples from all women subsequently enrolled. Thus, the inflammatory biomarkers were available for analysis from 91 women (Figure 1). Recruitment information for the parent trial⁴⁹ and the methodological design^{50,51} are described elsewhere. The experimental design employed 2 treatment groups; both receiving a comprehensive, 12-week CR program, with 1 group receiving a motivational behavioral enhancement exclusively for women with CHD. The institutional review boards of the university and the study hospital approved the study.

Women in the sub-study were recruited from 2006 to 2008. Inclusion criteria were 1) diagnosed with an acute myocardial infarction (AMI), angina, or having undergone coronary

artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) within the last year; 2) able to read, write, and speak English; and 3) willing and able to participate. The exclusion criteria were 1) health insurance coverage for less than 36 ECG-monitored exercise sessions; 2) cognitive impairment; 3) inability to ambulate; or 4) insertion of an automatic internal cardiac defibrillator (AICD) in the last year.

Measures

Clinical and Physiological Characteristics—Physiological assessments including risk factors, anthropomorphic measures, medication use, fasting lipids and glucose tests, and a symptom-limited exercise tolerance tests (ETT) were conducted at baseline and after CR completion. Using the modified Bruce protocol for the ETT,^{52–54} peak exercise capacity was expressed in units of metabolic equivalents (METS) where a MET equals 3.5 ml oxygen consumption per kg per minute. Blood pressure (BP) was measured with one calibrated automated oscillometric BP monitor (Datascope, Mahwah, NJ) according to established guidelines.⁵⁵ Body mass index (BMI) was calculated as weight (kg)/height (m²). Body fat composition was determined using the mean of three measures of skin folds taken at three sites (suprailium, triceps, and thigh). The percent of body fat was calculated from standardized tables.⁵⁶ Lipid profiles and serum glucose were measured after a 12-hour fast using the Cholestech LDX System.

The National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria were used to define MetS and comprises at least 3 of the following criteria: waist girth >88 cm, triglycerides >150 mg/dL; HDL-C <50 mg/dL; blood pressure (BP) >130 mm Hg systolic and/or >85 mm Hg diastolic; and fasting glucose >110 mg/dL.⁵⁷ Following the lead of those who recommend avoiding lost information inherent in dichotomization,^{58, 59} the individual MetS components were analyzed as continuous variables.

Biomarkers—Blood samples (5 mL) were obtained in heparinized tubes after a 12-hour fast. Samples were centrifuged at 3500 rpm for 25 minutes at 0° C and serum samples were then stored in 1.5 ml microcentrifuge tubes and immediately placed at –80°C until analysis. The Luminex 200 IS system, a laser-based fluorescent analytic system that is used in conjunction with LINCOplex Bio-assays (Millipore Corporation, St. Charles, Missouri), was used to analyze hsCRP, IL-6, TNF- α , and ICAM-1. All assays were analyzed according to manufacturers' protocols. All samples were run in duplicates and concentrations were analyzed using a 5-parameter logistic curve-fitting method. Measures of cytokines that were less than the minimum detectable concentration (<3.2 pg/mL) were set equal to half the detection level.⁶⁰

Serum hsCRP was measured using a LINCOplex Human Cardiovascular Disease kit. The minimum detectable concentration (sensitivity) is 6 pg/mL. The cutpoints of low risk (<1.0 mg/L), average risk (1.0 to 3.0) mg/L and high risk (>3.0 mg/L) correspond to tertiles of hsCRP in the adult population.⁶¹ Elevated hsCRP levels (>3.0 mg/L) add prognostic information to traditional risk factors of future CHD risk.^{62, 63} The Human Cytokine LINCOplex two-plex kit was used to measure TNF- α and IL-6 in serum samples. Sensitivities for TNF- α and IL-6 were 0.22 pg/mL and 0.79 pg/mL, respectively. ICAM-1 was measured using the Human Sepsis/Apoptosis LINCOplex kit with a minimum detectable concentration of 30.0 pg/mL. An overnight incubation of 18 hours at 4°C on a plate shaker set at 600 rpm was performed to provide better sensitivity for the analyses of TNF- α , IL-6, and ICAM-1. Manufacturer-provided quality controls for calculating intra- and interassay coefficients of variation (CVs) were used. The intra-assay CVs for hsCRP, TNF- α , IL-6, ICAM-1 were 8.0%, 8.0%, 13.6%, and 5.0, respectively. The interassay CVs for hsCRP, TNF- α , IL-6, ICAM-1 were 17.5%, 10.9%, 12.7%, and 8.7%, respectively.

Interventions

Traditional CR Intervention—The traditional CR program, nationally certified by the American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR), was delivered by nurses and exercise physiologists (EP) using a case management model. The exercise protocol consisted of combined aerobic exercise and upper body resistance training 3 days per week for 12 weeks. Exercise consisted of a 5 minute warm-up and 35–45 minutes of aerobic exercise (treadmill walking, cycling, or rowing) with exercise heart rates maintained at 60–85% of maximal heart rate calculated from their baseline ETT. Resistance training included wall-pulleys and hand weights followed by 5 minutes of cool-down exercises. Both the aerobic and resistance exercise training protocols were progressed weekly in duration and intensity according to participant's functional capacity, response to exercise, and rate of perceived exertion. Eight hours of education classes (1 hour each week), focusing on CHD risk factor modification, were provided by the CR personnel.

Gender-Tailored Intervention—The gender-tailored exercise protocol was identical to that of the traditional CR program except that participants exercised exclusively with women in their cohort and the time of the intervention was restricted to one time slot when the traditional CR facility was closed to avoid crossover contamination. The psychosocial intervention, guided by the Transtheoretical Model (TTM) of behavior change⁶⁴ and delivered with a motivational interviewing (MI) counseling style⁶⁵ was administered by female research nurses and EPs. Women were assessed for their motivational readiness to change regarding physical activity, stress reduction, and dietary modification. The TTM assessment provided an individualized 5-page report providing feedback on change processes relevant to the participant's stage of change for each behavior that were subsequently reinforced by their case manager. Participants received 1-hour individualized MI sessions at weeks 1 and 6 with a clinical psychologist or a clinical nurse specialist (CNS) formally trained in MI. The CNS and psychologist facilitated weekly psychoeducational classes, totaling 10 hours, focused on gender-based practice guidelines, relaxation exercises, and social support. Details of the intervention are described elsewhere.⁵⁰ Both groups received a 30 minute consultation with a dietician.

Data Analysis

Data were analyzed using SPSS version 17 for Windows (SPSS, Inc, Chicago, Ill). Descriptive statistics included means, standard deviations, Pearson correlations, and percentages. Categorical variables were compared using the χ^2 test, and continuous variables were compared using the *t*-test. ANOVA was used to compare baseline to post-test changes between the 2 treatment groups. All tests were 2-tailed and evaluated for statistical significance using an α of .05 criterion. The inflammatory biomarkers and triglyceride levels were logarithmically transformed for statistical analyses and then back-transformed to their natural units for presentation in tables.

Results

Baseline Characteristics

With a mean age of 61.6 ± 10 years (range, 42–82 years) most of the women were Caucasian (82%), married (51.6%), retired (49.5%), with $\geq$ high school education (93%). Women in this study qualified for CR because they had undergone either a PCI (48%) or CABG surgery (35.5%) or were diagnosed with an AMI (4.4%) or stable angina (12%). Medical record documentation revealed a previous AMI in 18%, a previous CABG in 8% and a previous PCI in 21% of participants. At baseline, women were taking evidence-based medications including β -blockers (78%), lipid lowering agents (92%), aspirin (88%), clopidogrel (67%), and angiotensin-converting enzyme inhibitors (32%). About 26% of

women were taking nonsteroidal anti-inflammatory agents and 6.6% were on estrogen replacement. There were no group differences in medication use and medication consumption remained stable over the study period. At baseline, women randomized to the traditional CR program were not different than those randomized to the gender-tailored program regarding lipid profiles, anthropomorphic indices, weight, or exercise capacity (Table 1). Groups also demonstrated similar distributions of the components of MetS and inflammatory biomarkers at baseline (Table 2). However, those in the traditional compared to the gender-tailored group had higher baseline triglyceride levels ($P<.05$).

Effects of Cardiac Rehabilitation on Physiological Characteristics

We evaluated the effects of moderate-intensity exercise on the physiological characteristics for the entire sample of 87 women who completed CR; there were no significant between group differences (Table 1). Participants had a mean weight loss of 3 ± 8.5 pounds, reduced their BMI by 0.6 ± 1.5 kg/m², and reduced their body fat by $2\pm9\%$ ($P<.05$ for all). The total sample achieved a 25% increased peak exercise capacity (2 ± 2 metabolic equivalents) and an increased treadmill time by 2 ± 2 minutes ($P<.05$ for both). The improved exercise capacity and weight loss was accompanied by a mean reduction in total cholesterol (TC) of 10.2 ± 34 mg/dL, a mean reduction in low-density lipoprotein cholesterol (LDL-C) of 8.4 ± 33 mg/dL, and a mean reduction in the TC/HDL-C ratio of 0.4 ± 1.2 ($P<.05$ for all). Compared to baseline, participants of the gender-tailored intervention demonstrated significant improvements in all physiological parameters. The traditional CR intervention, in contrast, led to no improvements in TC, HDL-C, TC/HDL-ratio, or percent body fat.

Influence of Cardiac Rehabilitation on Components of the Metabolic Syndrome

The effects of 12 weeks of moderate-intensity exercise on components of the MetS and the inflammatory biomarkers were examined next (Table 2). For the combined study group, CR led to mean reductions in triglycerides of 17 ± 44 mg/dL ($P<.05$), waist circumference of 3 ± 4 cm ($P<.05$), and systolic BP of 3 ± 14 mm Hg ($P<.05$). Improvements were not found for HDL-C, glucose, or diastolic BP. Compared to baseline, the gender-tailored participants had significantly reduced systolic and diastolic BP ($P<.05$) at follow-up with no detectable changes in the traditional group participants. Both interventions yielded similarly reductions in waist circumference ($P<.05$). The only between-group difference found was that the gender-tailored group had greater reductions in diastolic BP over time compared to the traditional group participants ($P<.05$).

The Influence of Cardiac Rehabilitation on Inflammatory Biomarkers

After CR participation, the combined study group demonstrated significant improvements in hsCRP ($P=.003$), ICAM-1 ($P=.027$), IL-6 ($P<.001$) and TNF- α ($P=.014$) (Table 2). Mean baseline hsCRP levels decreased 40% from 5.8 mg/L to 3.6 mg/L after CR. Baseline TNF- α levels of 10 pg/mL were also reduced by 40% to 6 pg/mL after CR, and IL-6 levels were reduced by 55.5%, from a mean of 18 pg/mL to 8 pg/mL. ICAM-1 was more modestly reduced by a mean of 29 ± 102 pg/mL (15%) after CR participation. The gender-tailored intervention produced significant reductions in all inflammatory biomarkers ($P<.05$ for all) while the traditional CR intervention led to lower hsCRP and IL-6 but not TNF- α or ICAM-1. The gender-tailored intervention led to greater reductions in ICAM-1 than the traditional CR intervention ($P<.05$).

To gain insight into differential effects of the 2 CR groups on the MetS components and inflammation we examined attendance by intervention group. The traditional CR participants attended a mean of 28 ± 13 (78%) of the prescribed 36 exercise sessions while women in the gender-tailored group attended a mean of 33 ± 9 (92%) ($F=4.285$, df (1, 89), $P=.041$). Compared to women in traditional CR, those in the gender-tailored intervention

also attended a greater percentage (88.5 ± 23 versus 62 ± 31) of prescribed education sessions ($F=20.794$, $df(1, 89)$, $P<.001$). All participants in the gender-tailored group completed the intervention while 4 in the traditional group did not; these noncompleters attended a mean of 6 sessions (range, 1–13).

Discussion

The major finding of this study is that 12 weeks of moderate-intensity exercise in the CR setting produces important improvements in markers of inflammation including hsCRP, IL-6, TNF- α , and ICAM-1 in women with CHD. Examination of the individual components of the MetS as continuous variables revealed that CR positively influenced abdominal obesity, triglyceride levels, and systolic BP. While both groups lost weight, only the gender-tailored group reduced their TC, LDL-C, and TC/HDL ratio. Both groups achieved significantly improved peak exercise capacity and treadmill time after completion of CR. Compared to traditional CR, the gender-tailored intervention was superior in reducing diastolic BP and ICAM-1 concentrations. Compared those in traditional CR, the gender-tailored intervention participants attended more prescribed exercise and education sessions. Explanations for greater attendance and reduced diastolic BP and ICAM-1 levels in the gender-tailored intervention remain speculative. The study was not designed to isolate the effect of any one of the intervention's multifaceted components on the outcomes. It is, therefore, unknown which intervention component led to the statistically significant differences on these variables. That the intervention used motivational interviewing, stage-matching, gender-tailoring, and social support may have synergistically improved some of the outcomes.

At baseline, most women were taking evidence-based medications to treat components of the MetS. Not surprising then, baseline levels of BP, triglycerides and glucose fell at or below the ATP III cutpoint criteria for MetS leaving little room for improvement after CR. This potential floor effect for various MetS components presents a challenge for demonstrating improved outcomes in secondary prevention settings where patients may enter CR with relatively well-controlled BP and lipid profiles. Reduced waist circumference was observed after CR participation. Had we dichotomized waist circumference according to the ATP III criteria (< 88 cm versus > 88 cm), this improvement would have been obscured because the mean value after CR remained above the somewhat arbitrary cutpoint of 88 cm.

Robust evidence links inflammation with central obesity and MetS,^{13, 19, 67} and with increased CHD risk.⁶⁸ Despite modest improvements in MetS components, we observed impressive reductions in the inflammatory protein and cytokine concentrations. The mechanism underlying these improvements remains elusive. While evidence exists that exercise was shown to independently lower CRP as much or more than statins,³⁵ others report a weak relationship between fitness and CRP in patients using medications that modify inflammation.⁶⁹ Independent of weight, regular muscle movement during exercise may modify inflammation locally while systemic inflammation is reduced through muscle-derived cytokines.³³ The anti-inflammatory effect of exercise in women with CHD may be even greater because of their lower baseline exercise capacity and higher inflammatory levels.⁴² Evidence points to an inverse relationship between inflammatory markers and cardiorespiratory fitness after adjustment for adiposity.⁷⁰ Even though the majority of our study participants were taking statins and aspirin therapy, they attained substantially improved inflammatory biomarkers; yet post-CR hsCRP remained in the high risk category (> 3 mg/L).

Our findings of reduced inflammatory biomarkers complement and extend the few studies that have examined the influence of CR on inflammation.^{31, 44–47} Our results support the premise that exercise training need not result in substantial weight loss to positively influence inflammation,^{30, 42, 45, 71} particularly in the CR setting where weight loss is typically minimal. Milani and colleagues^{30, 44} found that CR for 235 patients (32% women) led to a 36% reduction in hsCRP independent of weight changes. Goldhammer et al.⁴⁷ also reported that CR for 28 CHD patients (10 women) reduced hsCRP by 48% and IL-6 by 42%. Caulin-Glaser and associates⁴⁵ assessed the effects of CR on hsCRP in 172 patients with CHD (22% women). Though not stratified by gender, they found reductions in hsCRP from 5.7 to 2.7 mg/L. Lavie and colleagues⁴⁴ examined the effects of CR on hsCRP and MetS in 72 lean patients (BMI <25 kg/m²) and 73 obese patients (BMI > 30 kg/m²) with baseline hsCRP levels of 5.4 and 7.4 mg/L, respectively. After CR, the obese, but not the lean participants, attained a 43% reduction in hsCRP and a 1.5% reduction in BMI with little change in abdominal girth. This was accompanied by improvements in HDL-C (36.7 to 39.5) but no improvements in glucose, BP, or triglycerides.

Ades and colleagues⁴⁸ compared outcomes of 34 (8 women) participants randomized to a 5-month traditional CR program compared to 37 (5 women) randomized to a high-calorie-expenditure exercise protocol. While they found that the high-calorie-expenditure exercise resulted in double the weight loss and a 16% reduction in hsCRP, they found no group differences in the MetS components of BP, triglycerides, HDL-C or glucose. Our study expands on their work with our inclusion of only women who underwent moderate-intensity exercise. The generalizability of their results to women is tentative given the low exercise capacity in the majority of women enrolled in CR.⁷²

Limitations of this study merit consideration. First, data must be interpreted with caution because individuals receiving statins may show falsely low hsCRP concentrations.⁷³ Second, the baseline biomarker levels demonstrated greater variability than those obtained after CR. The reduction in all the biomarker levels after CR likely represents a restricted range effect. We found no relationship between statin or aspirin therapy and inflammatory biomarkers (likely restricted range). Third, we did not exclude patients with undiagnosed inflammatory processes such as periodontitis, or subclinical infections. Finally, there are important genetic and environmental determinants of each of the measured biomarkers and metabolic profiles for which we have not accounted.

Conclusions

Inflammation plays a key role in metabolic risk and the progression of CHD. While we found few between-group differences, both the gender-tailored and traditional CR programs were effective in reducing inflammatory biomarkers in women. Beyond the benefits of evidence-based medications, CR led to reductions in some components of MetS (waist circumference and triglycerides) but not others. The sustainability of the observed reductions in inflammation and the consequences for disease progression require closer examination. Our study supports the benefits of moderate-intensity exercise for reducing inflammation and central adiposity and improving cardiorespiratory fitness in women with established CHD. Identifying the gene-gene and gene-environment interactions that influence inflammatory biomarkers, obesity, and MetS will increase our understanding of the biological explanations for disease progression and responses to treatment.

Summary and Implications

- Cardiac rehabilitation improved measures of inflammation in women with coronary heart disease.

- Cardiac rehabilitation typically leads to minimal weight loss but improvements in body composition may not be a precondition for the benefits of exercise perhaps due to reduced visceral fat.
- Cardiac rehabilitation improved some but not all components of the metabolic syndrome.
- Cardiac rehabilitation for women significantly reduced the mean waist circumference although it remained above the recommended limit of 88 cm.

Acknowledgments

This study was sponsored through the following grants from the National Institutes of Health: RO1 NR007678 and RO1 NR007678-04S1.

References

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart Disease and Stroke Statistics--2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2008;119(3):e21–181. [PubMed: 19075105]
2. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement. *Curr Opin Cardiol* 2006;21(1):1–6. [PubMed: 16355022]
3. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112(17):2735–2752. [PubMed: 16157765]
4. Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. *Am J Cardiol* 2006;97(2A):3A–11A. [PubMed: 16675316]
5. Grundy SM. Metabolic syndrome: a multiplex cardiovascular risk factor. *J Clin Endocrinol Metab* 2007;92(2):399–404. [PubMed: 17284640]
6. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143–3421. [PubMed: 12485966]
7. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 2006;444(7121):881–887. [PubMed: 17167477]
8. Gami AS, Witt BJ, Howard DE, et al. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. *J Am Coll Cardiol* 2007;49(4):403–414. [PubMed: 17258085]
9. Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Inflammation, atherosclerotic burden and cardiovascular prognosis. *Atherosclerosis* 2007;195(2):e126–134. [PubMed: 17336309]
10. Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Impact of metabolic syndrome on atherosclerotic burden and cardiovascular prognosis. *Am J Cardiol* 2007;99(12):1623–1628. [PubMed: 17560864]
11. Schwartz GG, Olsson AG, Szarek M, Sasiela WJ. Relation of characteristics of metabolic syndrome to short-term prognosis and effects of intensive statin therapy after acute coronary syndrome: an analysis of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial. *Diabetes Care* 2005;28(10):2508–2513. [PubMed: 16186288]
12. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14 719 initially healthy American women. *Circulation* 2003;107(3):391–397. [PubMed: 12551861]
13. Yan E, Chen S, Hong K, et al. Insulin, hs-CRP, leptin, and adiponectin. An analysis of their relationship to the metabolic syndrome in an obese population with an elevated waist circumference. *Metab Syndr Relat Disord* 2008;6(1):64–73. [PubMed: 18370838]
14. Galassi A, Reynolds K, He J. Metabolic syndrome and risk of cardiovascular disease: a meta-analysis. *Am J Med* 2006;119(10):812–819. [PubMed: 17000207]

15. Majka DS, Chang RW, Vu TH, et al. Physical activity and high-sensitivity C-reactive protein: the multi-ethnic study of atherosclerosis. *Am J Prev Med* 2009;36(1):56–62. [PubMed: 19013748]
16. Feinberg MS, Schwartz R, Behar S. Impact of metabolic syndrome in patients with acute coronary syndrome. *Adv Cardiol* 2008;45:114–126. [PubMed: 18230959]
17. Khera A, McGuire DK, Murphy SA, et al. Race and gender differences in C-reactive protein levels. *J Am Coll Cardiol* 2005;46(3):464–469. [PubMed: 16053959]
18. Albert MA, Glynn RJ, Ridker PM. Effect of physical activity on serum C-reactive protein. *Am J Cardiol* 2004;93(2):221–225. [PubMed: 14715354]
19. Pischon T, Hu FB, Rexrode KM, Girman CJ, Manson JE, Rimm EB. Inflammation, the metabolic syndrome, and risk of coronary heart disease in women and men. *Atherosclerosis* 2008;197(1):392–399. [PubMed: 17681508]
20. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. *Circulation* 2004;109(6):714–721. [PubMed: 14970105]
21. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342(12):836–843. [PubMed: 10733371]
22. Kip KE, Marroquin OC, Shaw LJ, et al. Global inflammation predicts cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. *Am Heart J* 2005;150(5):900–906. [PubMed: 16290958]
23. Shlipak MG, Ix JH, Bibbins-Domingo K, Lin F, Whooley MA. Biomarkers to predict recurrent cardiovascular disease: the Heart and Soul Study. *Am J Med* 2008;121(1):50–57. [PubMed: 18187073]
24. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. *Lancet* 1998;351(9096):88–92. [PubMed: 9439492]
25. Athyros VG, Kakafika AI, Karagiannis A, Mikhailidis DP. Do we need to consider inflammatory markers when we treat atherosclerotic disease? *Atherosclerosis* 2008;200(1):1–12. [PubMed: 18420211]
26. Ridker PM, Silvertown JD. Inflammation, C-reactive protein, and atherothrombosis. *J Periodontol* 2008;79(8 Suppl):1544–1551. [PubMed: 18673009]
27. Ridker P, Rifai N, Koenig W, Blumenthal RS. C-reactive protein and cardiovascular risk in the Framingham Study. *Arch Intern Med* 2006;166(12):1327–1328. [PubMed: 16801524]
28. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. *J Intern Med* 2008;264(4):295–314. [PubMed: 18823504]
29. Ogawa H, Yasue H, Miyao Y, et al. Plasma soluble intercellular adhesion molecule-1 levels in coronary circulation in patients with unstable angina. *Am J Cardiol* 1999;83(1):38–42. [PubMed: 10073782]
30. Milani RV, Lavie CJ, Mehra MR. Reduction in C-reactive protein through cardiac rehabilitation and exercise training. *J Am Coll Cardiol* 2004;43(6):1056–1061. [PubMed: 15028366]
31. Milani RV, Lavie CJ. Prevalence and profile of metabolic syndrome in patients following acute coronary events and effects of therapeutic lifestyle change with cardiac rehabilitation. *Am J Cardiol* 2003;92(1):50–54. [PubMed: 12842245]
32. Mora S, Cook N, Buring JE, Ridker PM, Lee IM. Physical activity and reduced risk of cardiovascular events: potential mediating mechanisms. *Circulation* 2007;116(19):2110–2118. [PubMed: 17967770]
33. Kasisis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. *J Am Coll Cardiol* 2005;45(10):1563–1569. [PubMed: 15893167]
34. Kelley GA, Kelley KS. Effects of aerobic exercise on C-reactive protein, body composition, and maximum oxygen consumption in adults: a meta-analysis of randomized controlled trials. *Metabolism* 2006;55(11):1500–1507. [PubMed: 17046553]
35. Plaisance EP, Grandjean PW. Physical activity and high-sensitivity C-reactive protein. *Sports Med* 2006;36(5):443–458. [PubMed: 16646631]

36. Taylor RS, Brown A, Ebrahim S, et al. Exercise-based rehabilitation for patients with coronary heart disease: systematic review and meta-analysis of randomized controlled trials. *Am J Med* 2004;116(10):682–692. [PubMed: 15121495]
37. Wenger NK. Current status of cardiac rehabilitation. *J Am Coll Cardiol* 2008;51(17):1619–1631. [PubMed: 18436113]
38. Smith SC Jr, Allen J, Blair SN, et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation* 2006;113(19):2363–2372. [PubMed: 16702489]
39. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev* 2007;27(3):121–129. [PubMed: 17558191]
40. Huffman KM, Samsa GP, Slentz CA, et al. Response of high-sensitivity C-reactive protein to exercise training in an at-risk population. *Am Heart J* 2006;152(4):793–800. [PubMed: 16996860]
41. Mora S, Lee IM, Buring JE, Ridker PM. Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *JAMA* 2006;295(12):1412–1419. [PubMed: 16551713]
42. Nicklas BJ, Hsu FC, Brinkley TJ, et al. Exercise training and plasma C-reactive protein and interleukin-6 in elderly people. *J Am Geriatr Soc* 2008;56(11):2045–2052. [PubMed: 19016938]
43. You T, Nicklas BJ. Effects of exercise on adipokines and the metabolic syndrome. *Curr Diab Rep* 2008;8(1):7–11. [PubMed: 18366992]
44. Lavie CJ, Morshedi-Meibodi A, Milani RV. Impact of cardiac rehabilitation on coronary risk factors, inflammation, and the metabolic syndrome in obese coronary patients. *J Cardiometab Syndr* 2008;3(3):136–140. [PubMed: 18983328]
45. Caulin-Glaser T, Falko J, Hindman L, La Londe M, Snow R. Cardiac rehabilitation is associated with an improvement in C-reactive protein levels in both men and women with cardiovascular disease. *J Cardiopulm Rehabil* 2005;25(6):332–336. [PubMed: 16327525]
46. Kim YJ, Shin YO, Bae JS, et al. Beneficial effects of cardiac rehabilitation and exercise after percutaneous coronary intervention on hsCRP and inflammatory cytokines in CAD patients. *Pflugers Arch* 2008;455(6):1081–1088. [PubMed: 17906875]
47. Goldhammer E, Tanchilevitch A, Maor I, Beniamini Y, Rosenschein U, Sagiv M. Exercise training modulates cytokines activity in coronary heart disease patients. *Int J Cardiol* 2005;100(1):93–99. [PubMed: 15820291]
48. Ades PA, Savage PD, Toth MJ, et al. High-Calorie-Expenditure Exercise. A New Approach to Cardiac Rehabilitation for Overweight Coronary Patients. *Circulation* 2009;119 (20):2671–2678. [PubMed: 19433757]
49. Beckie TM, Mendonca MA, Fletcher GF, Schocken DD, Evans ME, Banks SM. Examining the challenges of recruiting women into a cardiac rehabilitation clinical trial. *J Cardiopulm Rehabil Prev* 2009;29(1):13–21. [PubMed: 19158582]
50. Beckie TM. A behavior change intervention for women in cardiac rehabilitation. *J Cardiovasc Nurs* 2006;21(2):146–153. [PubMed: 16601534]
51. Beckie TM, Fletcher GF, Beckstead JW, Schocken DD, Evans ME. Adverse baseline physiological and psychosocial profiles of women enrolled in a cardiac rehabilitation clinical trial. *J Cardiopulm Rehabil Prev* 2008;28(1):52–60. [PubMed: 18277832]
52. Finley CE, LaMonte MJ, Waslien CI, Barlow CE, Blair SN, Nichaman MZ. Cardiorespiratory fitness, macronutrient intake, and the metabolic syndrome: the Aerobics Center Longitudinal Study. *J Am Diet Assoc* 2006;106(5):673–679. [PubMed: 16647324]
53. Fletcher GF, Balady G, Froelicher VF, Hartley LH, Haskell WL, Pollock ML. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group. *Circulation* 1995;91(2):580–615. [PubMed: 7805272]
54. Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association

- Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 2002;106(14):1883–1892. [PubMed: 12356646]
55. Pickering TG, Hall JE, Appel LJ, et al. Recommendations for blood pressure measurement in humans and experimental animals: part 1: blood pressure measurement in humans: a statement for professionals from the subcommittee of professional and public education of the american heart association council on high blood pressure research. *Circulation* 2005;111(5):697–716. [PubMed: 15699287]
  56. Jackson AS, Pollock ML, Ward A. Generalized equations for predicting body density of women. *Med Sci Sports Exerc* 1980;12(3):175–181. [PubMed: 7402053]
  57. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001;285(19):2486–2497. [PubMed: 11368702]
  58. Stern MP, Williams K, Gonzalez-Villalpando C, Hunt KJ, Haffner SM. Does the metabolic syndrome improve identification of individuals at risk of type 2 diabetes and/or cardiovascular disease? *Diabetes Care* 2004;27(11):2676–2681. [PubMed: 15505004]
  59. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal: joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2005;28(9):2289–2304. [PubMed: 16123508]
  60. Helsel DR. More than obvious: better methods for interpreting nondetect data. *Environ Sci Technol* 2005;39(20):419A–423A.
  61. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107(3):499–511. [PubMed: 12551878]
  62. Ridker PM, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? *Circulation* 2004;109(23):2818–2825. [PubMed: 15197153]
  63. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. *Circulation* 2004;109(16):1955–1959. [PubMed: 15051634]
  64. Prochaska JO, Velicer WF. The transtheoretical model of health behavior change. *Am J Health Promot* 1997;12(1):38–48. [PubMed: 10170434]
  65. Miller, WR.; Rollnick, S., editors. *Motivational Interviewing: Preparing people for change*. 2. New York: Guilford; 2002.
  66. Prochaska JO, Velicer WF, Redding C, et al. Stage-based expert systems to guide a population of primary care patients to quit smoking, eat healthier, prevent skin cancer, and receive regular mammograms. *Prev Med* 2005;41(2):406–416. [PubMed: 15896835]
  67. Pou KM, Massaro JM, Hoffmann U, et al. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the Framingham Heart Study. *Circulation* 2007;116(11):1234–1241. [PubMed: 17709633]
  68. Beckman JA, Preis O, Ridker PM, Gerhard-Herman M. Comparison of usefulness of inflammatory markers in patients with versus without peripheral arterial disease in predicting adverse cardiovascular outcomes (myocardial infarction, stroke, and death). *Am J Cardiol* 2005;96(10):1374–1378. [PubMed: 16275181]
  69. Rahimi K, Secknus MA, Adam M, et al. Correlation of exercise capacity with high-sensitive C-reactive protein in patients with stable coronary artery disease. *Am Heart J* 2005;150(6):1282–1289. [PubMed: 16338272]
  70. Hamer M. The relative influences of fitness and fatness on inflammatory factors. *Prev Med* 2007;44(1):3–11. [PubMed: 17064760]
  71. Lakka TA, Lakka HM, Rankinen T, et al. Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. *Eur Heart J* 2005;26(19):2018–2025. [PubMed: 15987707]
  72. Ades PA, Savage PD, Brawner CA, et al. Aerobic capacity in patients entering cardiac rehabilitation. *Circulation* 2006;113(23):2706–2712. [PubMed: 16754799]

73. Genser B, Grammer TB, Stojakovic T, Siekmeier R, Marz W. Effect of HMG CoA reductase inhibitors on low-density lipoprotein cholesterol and C-reactive protein: systematic review and meta-analysis. *Int J Clin Pharmacol Ther* 2008;46(10):497–510. [PubMed: 18826864]
74. Lundgren JD, Malcolm R, Binks M, O'Neil PM. Remission of metabolic syndrome following a 15-week low-calorie lifestyle change program for weight loss. *Int J Obes (Lond)* 2009;33(1):144–150. [PubMed: 19015662]
75. Esposito K, Pontillo A, Di Palo C, et al. Effect of weight loss and lifestyle changes on vascular inflammatory markers in obese women: a randomized trial. *JAMA* 2003;289(14):1799–1804. [PubMed: 12684358]

Figure 1.
Flow of Participants in Study

Table 1
Physiological Characteristics Before and After Cardiac Rehabilitation by Intervention Group

Variable	Total Sample		Traditional (n=39)		Gender-Tailored (n=48)		F Time	F Group × Time
	Baseline	Post-CR	Baseline	Post-CR	Baseline	Post-CR		
Total cholesterol mg/dL	162±38	152±35	167±39	157±41	158±37	148±29	4.34*	<1
LDL-cholesterol mg/dL	92±34	84±29	95.2±33	89±34	89±34	79.5±24	4.24*	<1
Total/HDL cholesterol ratio	4±2	3.6±1	4.4±2	4±2	3.7±1.5	3.3±1	5.82*	<1
Body mass index, kg/m ²	32±7	31±7	32±7	31±7	32±7	31±7	4.71*	<1
Body weight, pounds	183±43	180±42	182±42	179±42	184±44	181.5±43	5.08*	<1
Percent body fat	38.88±3	38.27±4	38.75±3	38.41±4	38.98±3	38.16±4	7.21*	1.14
Resting heart rate, bpm	72±9	70±9	72±8	71±10	73±10	69±8	5.78*	1.68
Peak exercise capacity, METS	6±2	8±3	6±2	8.1±3	6±2.5	7.4±2	22.58*	1.74
Peak treadmill time, minutes	8.7±3	11±3	9±3	11±3.5	8.5±3	11±3	38.14*	<1

Abbreviations: bpm, beats per minute; CR, cardiac rehabilitation; HDL, high density lipoprotein; LDL, low density lipoprotein; METS, metabolic equivalent units
Results are presented as mean±SD.

* p <.05

Table 2
Metabolic Syndrome Components and Inflammatory Biomarkers Before and After Cardiac Rehabilitation by Intervention Group

Variable	Total Sample			Traditional (n=39)			Gender-Tailored (n=48)		
	Baseline	Post-CR	F Time	Baseline	Post-CR	F Time	Baseline	Post-CR	F Time
Metabolic Syndrome									
HDL-cholesterol mg/dL	43.4±13	45±13	2.66	41±12	42±11	<1	45±13	48±14	2.6
Triglycerides, mg/dL	132±65	115±55	12.97*	154±76 [†]	133±66	9.61*	113±47	101±39	3.76
Fasting glucose, mg/dL	101±25	103±22	<1	103±30	108±26	1.79	100±20	99±17	<1
Waist circumference, cm	100±15	97±15	39.59*	100±15	97±15	10.26*	100±15	97±14	34.16*
Systolic BP, mm Hg	118±12	115±12	4.54*	115±11	115±11	<1	121±12	115±12	7.91*
Diastolic BP, mm Hg	74±9	72±8	3.25	73±9	73±7	<1	75±9	71.5±8	8.35*
Inflammatory Biomarkers									
HsCRP, mg/L	5.8±8	3.6±5	9.67*	6±9	3.5±4	4.44*	6±8	4±5.5	5.33*
Interleukin-6, pg/mL	18±47	8±15	13.87*	17±45	7±7	5.39*	18±48	8±19	8.93*
TNF-α, pg/mL	10±22	6±5	6.23*	12±31	6±6	<1	8.5±9	5±4	6.99*
ICAM-1, pg/mL	211.5±117	177±81	5.04*	179±81	181±78	<1	228.5±134	173±83	14.11*
									7.75*

Abbreviations: BP, blood pressure; CR, cardiac rehabilitation; HDL, high-density lipoprotein; HsCRP, high-sensitivity C-reactive protein; ICAM-1, intercellular adhesion molecule-1; TNF-α, tumor necrosis factor alpha

Results are presented as mean±SD.

* P<.05;

[†] P<.05, baseline comparison between groups