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The Clinical Trial of Women On the Move through Activity and Nutrition (WOMAN Study)

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Abstract

The Women On the Move through Activity and Nutrition (WOMAN) Study is the first randomized clinical trial of nonpharmacological intervention designed to modify lipoproteins, weight loss and exercise among postmenopausal women using noninvasive measures of atherosclerosis as the primary endpoint. The trial was initially designed to test whether intervention as compared to health education would be more effective in slowing progression of subclinical atherosclerosis among women on hormone therapy (HT), estrogen or estrogen+progestin. It was designed and implemented prior to the results of the Women's Health Initiative (WHI). The trial was since modified to include women who had been on HT but went off after the results of the WHI were reported. Eligible women were between the ages of 52-62, had waist circumference ≥80 cm, low density lipoprotein cholesterol between 100-160 mg% and controlled blood pressure. The intervention is low in total and saturated fat, *trans* fats, higher in fiber and promotes loss of 7-10% of body weight and includes at least 150 minutes of physical activity per week. The study has recruited 508 women. The primary endpoints are change in extent of carotid intima media wall thickness as measured by carotid ultrasound, pulse wave velocity as a measure of vascular stiffness and coronary artery calcium using electron beam computed tomography. Body composition is measured by dual-energy x-ray absorptiometry.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in women. (1,2) Evidence-based guidelines direct providers to assess and intervene on key biological and lifestyle CVD risk factors, including elevated low density lipoprotein cholesterol (LDLc) and triglyceride levels, low high density lipoprotein cholesterol (HDLc), smoking, a sedentary lifestyle, obesity, and an eating pattern high in saturated fat and dietary cholesterol. (2,3)

The Women On the Move through Activity and Nutrition (WOMAN) study is the first randomized clinical trial to test the hypothesis that a nonpharmacological intervention among postmenopausal women currently or previously on hormone therapy (HT) would modify or reduce subclinical CVD, as measured by the amount of coronary artery calcium (CAC) and carotid intima-media thickness (IMT). The study was based on our previous observations from the Healthy Women Study (HWS) (4) and the Women's Healthy Lifestyle Project (WHLP) (5) that larger waist circumference (WC) and weight gain, especially as a woman moves from perito postmenopause, was associated with substantial increases in triglycerides, number of

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total and small LDL particles, a decrease in HDL particles and higher subclinical vascular disease among postmenopausal women. Other studies have shown that increased WC was also related to higher rates of heart attack. (6)

Levels of LDL, especially number of particles, apolipoprotein-B (ApoB), LDL size, lower HDL particles and higher triglyceride levels are associated with a higher prevalence of subclinical atherosclerosis (7), including CAC, greater carotid IMT and heart attack. (8) The extent of subclinical disease in carotid, coronary and lower extremity arteries are also associated with increased risk of CHD and stroke. (9,10)

We initially selected women on HT because of possible adverse effects of oral HT on lipoproteins, especially increase in triglycerides and small LDL particles and blood pressure (BP), particularly among women who had high WC, weight gain or insulin resistance. These adverse changes would blur the potential benefits of HT in decreasing risk of coronary artery disease, in spite of known reduction of LDLc and increased HDLc by HT.

The primary endpoints for the WOMAN study are measures of subclinical CVD, including: a) CAC as measured by electron beam computed tomography (EBCT); b) vascular stiffness as measured by arterial PWV; and c) carotid IMT. It is extremely unlikely that a clinical trial specifically focusing on lipid reduction to prevent hard endpoints, such as myocardial infarction, among women will be done because of substantial costs.

In recent years, six changes have occurred that strongly impact on approaches to the prevention of CVD in women: 1) newer methods of measuring lipoproteins and inflammatory markers; (11,12) 2) noninvasive imaging of arteries, especially the coronary, aortic and carotid; (13) 3) substantial reduction in the amount of saturated fat and cholesterol in the U.S. diet; (14,15) 4) increase in the prevalence of obesity, especially central obesity (16); 5) substantial decrease in the prevalence of cigarette smoking; (17) and 6) a marked increase in the extent of sedentary behavior. (18) The WOMAN study has attempted to utilize or impact on most of these factors.

Relatively few women until older ages (70+) are candidates for lipid-lowering therapy by current National Cholesterol Education Program (NCEP) guidelines. (19) The extent of subclinical atherosclerosis in the coronary arteries is low among women as compared to men, with over 50% of women at about age 62 having no CAC (20) and at very low risk of heart attack. (13) Prevention of the development and progression of atherosclerosis among postmenopausal women could have a major effect on CHD incidence and mortality, even to older ages.

The subclinical measurements are: 1) strongly related to CVD risk factors that are being modified in the WOMAN study, i.e. LDLc, triglycerides, WC, body mass index (BMI), HDLc (21); 2) related to clinical outcomes, as has been noted in many studies in both men and women (9,22,23,24); and 3) reduction or slowing of progression of carotid IMT by pharmacological intervention. (25,26)

We previously reported in our successful clinical trial of prevention of risk factor changes from peri- to postmenopause by diet and exercise intervention; that women in the intervention arm had slower progression of carotid IMT at follow up. (27)

Measurement of CAC is the best currently available noninvasive approach to measuring coronary atherosclerosis, at least in large primary prevention population samples. Only a few studies have evaluated the effects of lipid-lowering therapy on slowing progression of CAC. The results of these studies have been equivocal. (28,29) These studies, however, have focused on individuals with high CAC scores and had relatively short follow up. It is possible, however, that one could modify the extent of coronary atherosclerosis without showing any effects on

CAC, especially if plaque characteristics change, i.e. if there are reductions in cholesterol and fat in the plaque with no apparent change or even an increase in the calcium scores. The WOMAN study focused on the prevention of new CAC or progression among women with relatively low CAC scores. This has not been done in any other study.

The declining dietary intake of saturated fat (11% saturates in the U.S. diet) requires fairly intensive interventions to further lower LDLc levels, with greater emphasis on increasing polyunsaturates, weight loss and soluble fiber and plant-based eating patterns. (30,31) The currently recommended American Heart Association and National Heart, Lung, and Blood Institute dietary recommendations have little effect on reduction of LDLc for most women. (32) Similarly, raising HDLc by nonpharmacological approaches is difficult and requires substantial increases in exercise and weight loss. (33)

We have also previously reported that weight loss among peri- and postmenopausal women is associated with both loss of bone and lean body mass. (34) Weight loss is a major risk factor for sarcopenia among older women. The WOMAN study includes measures of body composition and changes in sex-steroid hormone levels.

Methods

Subject Selection

Five hundred and eight postmenopausal women were recruited for this five-year trial, primarily by direct mailing from selected zip codes in Allegheny County, Pennsylvania, from April 2002 to October 2003. Eligible women were between the ages of 52 and 62 and had to be willing to be randomly assigned to either an intervention or comparison group. Eligibility criteria are listed in Table 1.

Initial entry criteria for the WOMAN study required a potential participant to have a history of at least two years on HT. However, in response to the WHI findings released during the recruitment phase of this study, we modified our eligibility criteria to include women with a recent history of HT use, as it was deemed unethical to continue requiring potential participants to be on the drug. (35,36) As a result, 204 women (40%) were not on hormones at baseline, with a median time off HT prior to entry of seven months.

These changes in eligibility resulted in a valuable and timely opportunity to investigate the lifestyle intervention for reducing the risk of CVD in women continuing on HT, as well for those in whom it had been discontinued, a large segment of postmenopausal women in the population. Women who had stopped HT may have a substantial increase in LDLc and possibly decline in HDLc that could put them at higher CVD risk.

Eligibility Visits

Visit 1: Baseline screening visit Eligible women based on return of initial mailings had a telephone interview and were then invited to attend two screening visits during which eligibility was further assessed, including biochemical and physical parameters. At Visit 1, informed consent was obtained, followed by BP measurement (<160/95 mmHG at initial screening and <140/90 mmHG at randomization on or off drug therapy), and measurement of WC (>80 cm), height, weight and BMI (25-39.9 kg/m^2). A Long Distance Corridor walk was completed in order to ensure that the potential participant could safely take part in a physical activity program. (37) Medical and drug use history, vitamin/mineral and supplement use, physical activity levels (Visit 1 or 2), alcohol consumption, and recent weight history were also taken. Participants completed the Beck Depression Inventory (BDI) (38) and those with a score <20 were eligible. Screening for eligibility based on fasting LDLc occurred during the visit; aliquots for further analysis were stored at −60° C.

Visit 2: Final eligibility and randomization At Visit 2, carotid ultrasound and arterial PWV were performed. CAC was measured using EBCT. Dual-energy x-ray absorptiometry measurements for bone mineral density (BMD) were taken; percent body fat and lean body mass calculations were obtained.

A three-day food record was also assigned for return at the second visit. Although not used for study data, the food record was used as a measure of adherence to instructions and willingness to self-monitor, as the latter is a critical behavior change tool used in the intervention. The Diet Habit Survey (DHS) (39), designed to identify eating habits and measure changes in intake of cholesterol, saturated fat, complex carbohydrate, and salt, was also self-administered and returned at Visit 2. Nutrient intake at baseline and follow-up is quantified by self-administration of a food frequency questionnaire (FFQ). A wide variety of food models are displayed for the participant to enhance accuracy of portion size estimation. The Fred Hutchinson Cancer Research Center FFQ (version GSEL, used for assessing intake in healthy adult populations) is used. (40) Both frequency of consumption and amount consumed over the past six months are assessed. The FFQ and DHS were re-administered at six months and yearly thereafter. Psychological questionnaires were also administered annually.

Questionnaires assessing psychosocial and quality of life parameters were administered prior to the second visit as well, including BDI (38), Cohen Perceived Stress Scale (41) and MOS short form health survey. (42,43)

A block randomization design was prepared by the statistician; sealed, numbered envelopes containing the assignment to intervention or control group were opened sequentially at the randomization interview upon finalizing eligibility. Volunteers were randomly assigned to a Health Education (HE) (comparison) group or Lifestyle Change (LC) (intervention) group.

Study Design

The intervention has a strong theoretical foundation. It uses an empirically-based cognitive-behavioral approach to promote the adoption and maintenance of a heart healthy lifestyle including weight control and a strong emphasis on physical activity (44,45). Examples of specific key behavioral strategies included: self-monitoring, goal setting, stimulus control, problem solving, cognitive restructuring, relapse prevention, social support, and motivational techniques. The design incorporates collection of lifestyle and outcome measures both at baseline and at 6-, 18-, 30-, 42-, and 50-month follow-ups.

Lifestyle Change Group—The WOMAN study utilizes and builds on our previous studies (such as the WHLP, the WHI and the Diabetes Prevention Program[DPP]). The specific intervention targets are:

A. Diet

1. A reduction in total, saturated, *trans* fat, as well as cholesterol, from meat, dairy products, fats and oils, baked goods, and snacks: It is well-accepted that reductions in saturated fat and dietary cholesterol intake lead to beneficial changes in serum cholesterol levels. (46) Consistent with NCEP Adult Treatment Panel III (ATP III) guidelines (2), saturated fat is limited to less than 7% of total energy, or less than 10 grams per day. Women were initially started on a 17% total and 4% saturated fat diet with the assumption that they would gradually increase to 7% saturated fat intake. Intake of *trans* fatty acids are kept low by avoiding hydrogenated oils predominant in baked goods, snacks and solid vegetable fats.

2. A reduction in total energy intake to1300 calories daily (1500 kcal when baseline body weight is >175 lbs) to support a 10% loss of weight and a decreased WC within the first six months: Modest weight loss optimizes plasma lipids, whereas subjects with a higher BMI have reduced HDLc levels and smaller LDL particles. (47) Intentional weight loss from a six-month diet was found to predict lower incidence of CVD over 4 years. (48) WC is independently associated with risk of CVD in women (49).

3. An increase in the use of foods high in soluble fiber: The ATP III recommends inclusion of dietary sources of viscous (soluble) fiber. Five to 10 grams soluble fiber reduces LDLc by approximately 3%-5%. The effect is likely related to their gel-forming properties, including an increase in binding of bile acids. Brown and colleagues, in their meta-analysis of 67 clinical trials, found that various soluble fibers promote lipid lowering, including oats, psyllium and pectin (50). A variety of food sources, such as oat bran, barley, and legumes are emphasized in the WOMAN eating pattern and recipes.

4. Promotion of nutrient-dense, high-volume, low calorie foods such as fruits, vegetables and whole grains: A significant inverse association between fruit and vegetable intake and CVD risk was found in the Women's Health Study (51). The insoluble components of whole grains, such as corn and wheat bran, appear to lower triglycerides. Work by Rolls and colleagues (52,53) suggests that lowering the energy density of eating patterns while promoting increased volume at meals through inclusion of water-rich fruits, vegetables and grains is associated with better diet quality, lower energy intakes, and decreased body weight. In order to demonstrate these principles, traditional recipes are reworked to include low density ingredients to boost volume and add a new focus to the weight loss modality. This reinforces the message that participants can consume satisfying portions of low energy density foods with fewer calories.

5. Inclusion of selected functional foods such as stanol ester-containing margarines, soy products and sources of n-3 fatty acids: Two to three grams per day of plant stanols/sterols are recommended in the ATP III report; evidence suggests these plant derivatives will lower LDL by 6% to 15% (54-56). Soy-based products are used to replace foods high in saturated fat, for example, by substituting soy-based crumbles for ground beef. Use of broiled or baked fish and flaxseed meal are encouraged to increase intake of omega-3 fatty acids as data suggest that higher intakes reduce risk for coronary events and mortality, possibly through beneficial effects on arterial compliance and vascular resistance; these fatty acids also reduce triglyceride levels (57-60).

The program is primarily group-based and is facilitated by a multi-disciplinary team of nutritionists, exercise physiologists, and psychologists. Contact is frequent throughout the program, with 40 visits the first year and a minimum of monthly meetings during Year 2 and beyond.

B. Physical Activity Intervention

Physical activity in conjunction with reduced calories and fat intake is the best combination for decreasing weight (preferentially decreasing centrally distributed fat) and to improving insulin sensitivity. Furthermore, physical activity has been shown to play an important role in long term weight maintenance. Therefore, we incorporated both diet and exercise into our intervention program. The basic design for the physical activity portion of the intervention

program is partially based upon our experience with the DPP (61) and previous clinical trials of walking older women, the Walking Women Follow-up (62) and WHLP. (44) We implemented a rigorous, stepped care approach to reach 150 min/week as the standard minimum goal for all women. Women who reach the minimum goal and who are willing will be advanced to 180 min/week , then to 240 min/week to give women progressively challenging physical activity targets. Aerobic types of activity that require the use of large muscle mass such as brisk walking are the primary types of physical activity currently recommended because of their known benefits in improving the cardiovascular risk profile. However, the benefits of incorporating strength training into an overall activity regimen (that includes aerobic activity) for the prevention of bone loss are now being recognized. Therefore, as an adjunct to the aerobic activity, we include strength training into the activity intervention portion of the study. Based on our previous work, we feel confident that participants can achieve these goals.

Health Education Group—A “core” education series of six seminars is offered during the first year of participation. These sessions are led by experienced health professionals and focused on topics in women's health. Contact is maintained by means of seminars offered several times a year, as well as via clinic visits that are held throughout the remainder of the study. Most of the information focuses on women's health and not specifically on CVD risk factors and drug therapy.

Monitoring of Interventions during the Trial at Yearly Intervals

Prior to baseline Visit 2 and at six months following randomization and annually thereafter, physical activity is monitored for seven days in a seven-day diary; activities such as walking, gardening, tennis, bowling, golf, etc. that occurred in 10-minute bouts or longer are recorded daily. Physical activity assessment continues with administration by trained personnel of the Modifiable Activity Questionnaire (MAQ), which assesses past year occupational and leisure activities, as well as extreme levels of inactivity due to disability. (63)

Laboratory Measurements

At baseline, six months and annual follow-up visits, total cholesterol, HDLc, and triglyceride concentrations are determined by conventional enzymatic methods from fasting (12-hour) blood samples. LDLc level is estimated by the Friedewald equation. Lipoprotein subclasses are determined by NMR spectroscopy (LipoScience Inc, Raleigh, NC), as previously described. (64)

Subclinical Measurements

CAC—An Imatron C-150 Scanner (Imatron, South San Francisco, Calif.) is used to obtain 30 to 40 contiguous 3-mm-thick transverse images of the heart, as previously described (20). CAC scores are calculated according to the Agatston method. The EBCT scans from this laboratory had high reproducibility, with an intraclass correlation of 0.99 (20).

Bone Mineral Density and Body Composition—The BMD of the posterior anterior lumbar spine (L1-L4) and hip (femoral neck, trochanter, and intertrochanter space) and whole-body soft tissue composition are measured by dual-energy X-ray absorptiometry (DXA) with the array mode (Hologic QDR 4500 (Discovery); QDR System Software Version 12.3; Hologic Inc., Waltham, MA) at the second screening visit. (34)

Carotid Ultrasound—Images are taken from the near and far walls of the distal common carotid artery (one centimeter proximal to the carotid bulb), and the far walls of the carotid bulb (the point where the near and far walls of the common are no longer parallel, extending to the flow divider) and the internal carotid artery (from the flow divider to 1 cm distal to this

point). (65) IMT measures were performed by electronically tracing the lumen-intima interface and the media-adventitia interface across a 1 cm segment. The computer then generates one measurement for each pixel over this area, for a total of about 140 measures. The mean of all average readings across the eight locations (four on each side) comprises the average IMT. We also calculated the mean of the maximum reading from each segment. The common carotid inter-adventitial diameter is read in the same way using the adventitial-medial interface on the near wall and the medial-adventitial interface on the far wall.

Pulse Wave Velocity (PWV)—PWV is measured by taking simultaneous recordings of the arterial flow waves from the right common carotid and right femoral artery using unidirectional transcutaneous Doppler flow probes (model 810-a, 8.9 mHz, Parks Medical Electronics Inc, Aloha, Ore.). (66,67) The PWV is calculated by dividing the distance traveled between transducers by the time of pulse wave travel. Output from the Doppler probes is captured and stored in a computer system for later scoring using a program developed by the National Institute on Aging.

The PWV measures are automatically generated using a noninvasive and automated waveform analyzer (Colin Co., Komaki, Japan). (68,69) This device records the phonocardiogram, ECG, and volume pulse form and arterial BP at the left and right brachial and ankles. It also records the carotid and femoral pulse waveform using multiarray tonometers.

Women are not provided the results of these subclinical measurements, i.e. primary outcome, except for seven women who were excluded from the trial because of very high CAC scores over 300 Agatston units.

Statistical Analysis

Analysis is planned under the intention-to-treat principle. The limitation of this approach is that women will drop out with endpoint data missing. Based on our previous studies, we expect to retain 90-95% of women by the Year 5 follow-up examination. We will examine any potential differences between women who eventually drop out and those who remain. Each of the subclinical measurements will be analyzed separately and statistical analysis and power estimations are provided separately. The measures, however, are markers of atherosclerosis and vascular disease. Therefore, consistency in changes in the measures will be of considerable importance.

There are no previous studies that have evaluated these endpoints in a nonpharmacological intervention study, especially in relatively healthy women. Our sample size estimates are based on cross-sectional and longitudinal data from observational studies.

Our primary outcome is progression of subclinical disease from baseline to five year follow-up, as compared between the two treatment groups. The primary outcomes are changes in PWV, carotid IMT and CAC. The rate of progression of PWV and carotid IMT will be measured as the difference between the Year 5 and baseline values. Prior data has shown that these changes are normally distributed. We will evaluate the mean change using *t*-tests under the null hypothesis of no differences between women in the intervention versus comparison group. Using linear regression analysis, we will further adjust for baseline covariates that might affect progression of subclinical disease measures. For example, we would be able to determine whether HT use modulates the effects of our intervention.

The rate of progression of coronary and aortic calcium as measured by EBCT between the intervention and comparison groups cannot be simply represented as a difference score. For change in CAC, we will perform separate analyses for women with a zero CAC score at baseline and for those with >0 baseline CAC score. Half of our women have zero CAC at baseline. For

these women, the outcome will be dichotomous (new CAC vs. no CAC) and we will use Chi-square statistical tests to compare women in the intervention versus the comparison group or logistic regression when adjusting for important covariates that might affect progression, such as the use of lipid-lowering drug medications and changes in WC. If a woman, on the other hand, has nonzero CAC at baseline, progression over time is highly skewed and dependent on baseline values. Some investigators have suggested calculating the rate of change as the difference between the logs of the baseline and outcome measures. This is equivalent to a ratio between the values of time 1 and time 2. This procedure normalizes the relationship between baseline and change values.

We plan to test the transformation approach suggested by Hokanson, et al. (70) with progression in CAC calculated as the difference between the five-year score and the square root of the baseline score. This transformation combines both the benefits of log transformation with the elimination of heterogeneity of variances, thus giving an unbiased comparison of change in CAC over time across the range of CAC scores. We will use *t*-tests to compare changes in the LC versus the HE groups and linear regression to adjust for potential confounding factors.

Sample Size Considerations

There are no previous studies that have evaluated these endpoints in a nonpharmacological intervention study, especially in relatively healthy women. Our sample size estimates are therefore based on cross-sectional and longitudinal data from observational studies. Overall, we determined that 508 was an adequate number to detect these changes, as follows.

CAC—For change in coronary calcification, we will perform separate analyses for women with a zero CAC score at baseline and for those with >0 baseline CAC score. In the WOMAN study, there are 248 women (49%) with a baseline total CAC score of zero. Prior results from the HWS have shown that in postmenopausal women with CAC=0 Agatston units, new CAC is 6% per year, or 30% over five years. We expect that an intensive intervention will reduce the incidence of new CAC by at least 50%. Thus, assuming at least 100 women per intervention group, if the five-year incidence is 30% in the HE women, we will be able to detect an incidence of 15% with 72% power, and an incidence of 13% with 84% power in the LC group.

If the five-year incidence is 25% in the HE women, we will detect an incidence of 10% with 80% power and 9% with 85% power in the LC group. We will also use a Chi-square test of independence to determine if the percent of women progressing to CAC is constant across the three HT groups. We do not expect differences in the women in the HE group. If we perform this analysis only in the women in the LC group (n=100), we would have 80% power to detect an effect size of 0.31. This corresponds to a Chi-square of 10.24 with 2 degrees of freedom and is considered a medium effect size.

We also have 251 (49%) participants with baseline CAC scores >0 and <400 (an additional 8 women with CAC>400 will be excluded from the analysis but not study participation. For women with CAC, the rate of progression is a function of baseline CAC values. Based on our HWS findings, we expect women with a baseline CAC 1-5 to have a five-year increase of 16.2; for a baseline CAC >5-10 the expected 5-year increase is 51.4; for a baseline CAC >10-200 the increase is 123.1; and for a baseline CAC >200 the increase is 514.9. The mean baseline CAC in the WOMAN study was 27.68±52.16. Based on the baseline WOMAN CAC scores and projected rates from the HWS study, we would expect a mean five-year CAC for women not receiving an intervention to be 93.14±112.52. As outlined above, change in CAC will be calculated as mean square root values, with a mean projected change of 4.52±1.79 in the control women. The LC group will need to have a reduction in the rate of CAC progression of at least 29% to be detected with 80% power. A meaningful outcome will be a 33% reduction in the

rate of CAC increase in women undergoing an intensive lifestyle intervention program. We will be able to detect this reduction with 90% power.

Carotid IMT—Our calculations are based on published data from 160 perimenopausal and postmenopausal WHLP participants (27) who were randomized to either a dietary and exercise intervention or an assessment-only control group. The annual change in bulb IMT was 0.0074 for the active intervention group and 0.0207 for the control group. We would have 84% power to detect the reported difference between the two treatment groups. We would detect a difference of 0.017 among the HT groups at 80% power. The change in the average IMT was 0.0041 in the intervention group and 0.0078 in the control group (SD 0.022). For the average IMT, we would need an annual change of 0.0016 in the intervention group to be detected with 80% power. Based on prior data, we anticipate that this is a reasonable expectation.

PWV—We expect the intervention to acutely affect functional changes in the arteries while remaining relatively constant in the controls. Our baseline assessment of PWV show this measure to be relatively normally distributed (with a few large outlyers), with a mean of 902 cm/sec (SD 255). If we assume no change in the HE group, we would have 80% power to detect about a 70 cm/sec difference (lower) in the LC as compared to the HE group at the end of the study . The study will have 99% power to detect a mean decrease to 793 cm/sec in the LC group. This value is still above those found in the older WHLP participants and would therefore be clinically important and feasible.

The estimation of power for the endpoints (triglycerides, WC, CRP and weight) were based on data from HT users in the HWS. At a two-sided alpha of 0.05 and 80% power, we would be able to detect differences of 20 mg triglycerides, 5 cm WC, 1 mg/l change in CRP, 10 lb weight loss.

Baseline Characteristics of Participants

The population is primarily Caucasian (88%). They are well-educated, with nearly half attending one to four years of college, and more than one-quarter having graduate degrees. (Table 2) The percentage of postmenopausal women that are black in Allegheny County is also relatively low and consistent with the distribution by race in the study. The distribution of risk factors by randomization group is shown in Table 2. There are no statistical differences in socioeconomic status and risk factor at baseline by randomization group (HE versus LC).

Women who were nonhormone users at baseline had higher total cholesterol, much higher LDLc, lower triglycerides and HDL, especially medium HDL particles. In spite of the lower LDLc measured chemically among women on HT, there were no significant differences among HT users or nonusers in total LDL particles and small LDL particles. (not shown)

The distribution of key risk factors by WC quartiles is shown in Tables 3 and 4. Higher WC is associated with greater levels of glucose, insulin, BP, triglycerides, total and small LDL particles, and lower large HDL particles and chemical HDLc measurements. (Tables 3 and 4) Results were generally similar for the HE and LC groups.

The distribution of CAC and carotid IMT was similar by randomization groups. (Table 5) Eight women who had CAC score >400 Agatston units (6 in LC, 2 in HE) and were excluded from the trial analyses because it would be unethical not to recommend lipid lowering therapy and one woman had an unreadable EBCT study. The prevalence of zero CAC was lower among women on HT as compared to those not on HT at entry, 54% as compared to 42% (p=0.03), distribution of CAC between HT users and nonusers (Chi-square test).

Discussion

The WOMAN study is the first large randomized trial to use noninvasive methods to evaluate nonpharmacological interventions in relatively healthy women. The incidence of CHD is low among women until older ages, 70+. Clinical trials for women with CHD endpoints either include very large sample sizes, such as in the WHI (71), or secondary prevention after heart attack. The WHI did not specifically focus on lifestyle intervention to reduce CHD risk and reported only small changes in lipoproteins and no difference between intervention and comparison group for CHD incidence or mortality.

Interventions that focus on a combination of changes in the composition of the diet, specifically very low saturated fat and *trans* fat, higher intake of omega-3 fatty acids and viscous fiber, combined with weight reduction and physical activity may be the best nonpharmacological approach to reduce atherosclerosis and CHD risk for many women. Maximizing adherence to these interventions over time is a challenge. The WOMAN study will be the first clinical trial to utilize a nutrition and physical activity intervention to reduce CV risk factors, then hopefully subclinical measures of atherosclerosis, in a relatively healthy population of women who are currently or have been on HT – a study cohort reflecting a large number of women in the U.S.

Prevention of the development and early progression of atherosclerosis in men and women will have a far greater effect on CHD incidence than treatment or secondary prevention trials. Nonpharmacological trials for women are especially important, given the results of HT trials with associated increased risk of stroke and possibly dementia and cancer. Women at very low risk for subsequent CHD can be identified, even during the premenopausal period, based on a constellation of risk factors and lifestyles. (72,73) However, there are very few such women who fit these criteria for low risk. Whether reduction of risk factors to these lower levels will be beneficial in terms of lower incidence of CHD is not known.

Changes in diet and physical activity and weight loss are recommended to reduce the risk of CHD for both men and women. (74) There is, however, no clinical trial evidence at the present time that these interventions, as recommended, reduce the risk of heart attack either in men or women, especially in postmenopausal women. A potential part of the problem may be the inability to substantially reduce the LDLc or raise the HDLc, except by very intensive dietary intervention and exercise. (75,76) Long term weight reduction and substantial increases in activity are also difficult to maintain. (77) A second problem is the likelihood that these nonpharmacological interventions may be less effective among women who already have extensive atherosclerosis, i.e. older postmenopausal women. (35,36)

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Table 1

Eligibility criteria

- Waist Circumference ≥ 80 cm
- 52-62 years
- LDLc between 100 and 160 mg/dl
- BMI 25-39.9 kg/m2
- Blood Pressure < 160/95 mmHg
- Beck Depression Inventory Score < 20
- No diagnosis of psychotic disorder
- No current use of cholesterol-lowering medication
- No diagnosis of diabetes or use of medication to treat diabetes
- Successful completion of 400-meter corridor walk test (heart rate ≥ 40 and ≤ 135 beats per minute throughout)
- Willingness to participate in either group

Table 2

Baseline sociodemographics and risk factors of study population

Baseline Characteristic	Total	HE (n=255)	LC (n=253)	*P*
Mean age at study entry	57	57	56	0.34
Race (% Caucasian)	88	87	89	0.41
Education				
% high school graduate	18	20	16	0.15
% college (>0 to 4 yrs)	53	49	57	
% graduate school	28	30	25	
Married (%)	68	66	69	0.14
Employed for wages (%)	79	78	79	0.78
Risk Factors		**Mean (SD)**		
BMI (kg/m^2)	30.8 (3.8)	30.9 (3.8)	30.6 (3.8)	0.29
Systolic BP	124.1 (76.7)	124.6 (13.6)	123.6 (13.4)	0.42
LDL (mg/dl)	128.0 (25.2)	129.3 (26.6)	126.6 (23.7)	0.23
HDL (mg/dl)	60.0 (14.2)	60.5 (14.1)	59.5 (14.3)	0.23
Triglycerides (mg/dl)	143.0 (75.0)	140.6 (76.1)	145.2 (73.8)	0.49
Total cholesterol (mg/dl)	212.7 (24.4)	217.8 (29.5)	215.3 (26.3)	0.31
WC (cm)	105.9 (11.2)	106.3 (11.4)	105.5 (11.1)	0.41
HT use (%)	59.8 (n=304)	55.7	64.0	0.06
Fasting glucose	25.3 (9.3)	95.8 (9.7)	94.7 (9.0)	0.16

Table 3

Distribution of risk factors and baseline characteristics by quartiles of waist circumference (WC) at baseline (Health Education group only)

	WC (cm)				
	<98	**98-104**	**104-113**	**>113**	**P test for linearity by WC**
N	65	57	66	67	(T=255)
Age (years)	57	57	57	57	0.12
Weight (lbs)	158	171	184	209	0.000
BMI (kg/m^2)	28	29	31	35	0.000
Systolic BP (mmHg)	122	123	123	129	0.07
Fasting glucose (mg)	94	95	94	100	0.002
Insulin (ΦIU/ml)	13	13	14	17	0.000
HDLc (mg%)[1]	61	62	62	57	0.17
LDLc (mg%)[1]	129	132	128	129	0.83
Triglycerides (mg%)[2]	129	142	138	154	0.87
NMR-determined lipoprotein subclass measures					
HDL particles (μmol/L)	35	35	35	35	0.78
Large HDL particles (mol/L)	8	8	8	7	0.03
Small HDL particles (mol/L)	24	25	25	25	0.55
LDL particles (n/mol/L)	1368	1372	1431	1440	0.15
Small LDL particles (nmol/L)	681	707	709	793	0.18
Large LDL particles (nmol/L)	644	625	674	600	0.52

[1] To convert to mmol/L multiply by 0.0259

[2] To convert to mmol/L multiply by 0.0113

Table 4

Distribution of risk factors and baseline characteristics by quartiles of waist circumference (WC) at baseline (Lifestyle Change group only)

	WC (cm)				
	<98	**98-104**	**104-113**	**>113**	**P test for linearity by WC**
N	58	70	66	59	(T=253)
Age (years)	57	57	57	57	0.43
Weight (lbs)	156	167	185	209	0.000
BMI (kg/m^2)	27	29	32	35	0.000
Systolic BP (mmHg)	132	121	126	125	0.07
Fasting glucose (mg)	93	93	94	98	0.002
Insulin (ΦIU/ml)	10	12	14	17	0.000
HDLc (mg%)[1]	63	62	56	57	0.006
LDLc (mg%)[1]	123	129	128	125	0.69
Triglycerides (mg%)[2]	137	137	155	152	0.14
NMR-determined lipoprotein subclass measures					
HDL particles (μmol/L)	36	34	34	36	0.93
Large HDL particles (mol/L)	9	8	7	7	0.002
Small HDL particles (mol/L)	24	23	25	26	0.006
LDL particles (n/mol/L)	1317	1378	1414	1435	0.02
Small LDL particles (nmol/L)	617	669	756	766	0.02
Large LDL particles (nmol/L)	664	669	610	625	0.14

[1] To convert to mmol/L multiply by 0.0259

[2] To convert to mmol/L multiply by 0.0113

Table 5

Comparison of subclinical measures by Health Education (HE) and Lifestyle Change (LC) groups at baseline

Coronary artery calcium	**HE N (%)**	**LC*** **N (%)**	***P*†**
0	124 (48.4)	124 (49.4)	
1-10	80 (31.4)	80 (31.7)	
11-100	41 (16.1)	30 (11.9)	
100+	10 (3.9)	18 (7.1)	
T	255 (100)	252 (100)	0.26
	Mean (SD)	**Mean (SD)**	
Mean average carotid intima media thickness	0.72 (0.10)	0.71 (0.09)	0.17
Mean maximal carotid intima media thickness	0.91 (0.14)	0.90 (0.14)	0.36

*1 person missing EBCT measurement

†Chi square or *t*-tests for differences between HE and LC groups.