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# A Dietary and Exercise Intervention Slows Menopause-Associated Progression of Subclinical Atherosclerosis as Measured by Intima-Media Thickness of the Carotid Arteries

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**OBJECTIVES** The object of this study was to assess the effects of menopause and a diet/exercise intervention on subclinical atherosclerosis progression.

**BACKGROUND** Subclinical atherosclerosis has been linked to higher coronary heart disease and stroke rates and is greater among postmenopausal women according to cross-sectional analyses. Whether menopause is associated with an accelerated progression of subclinical disease is unknown, as is the extent to which lifestyle intervention can alter the course of progression.

**METHODS** Intima-media thickness (IMT) measures of the common carotid artery (CCA), internal carotid artery (ICA), and bulb segments of the carotid arteries were measured twice during the course of 4 years in 353 women from the Women's Healthy Lifestyle Project, a dietary and exercise clinical trial designed to prevent adverse risk factor changes through the menopause. A third measure was obtained 2.5 years later for 113 women.

**RESULTS** The progression of IMT was observed for the average of all segments (AVG), the CCA, and the bulb (0.007 mm/year, 0.008 mm/year, and 0.012 mm/year; $p < 0.01$ for all), but not for the ICA. Among controls, menopause was associated with accelerated IMT progression (0.003 mm/year for premenopausal women vs. 0.008 mm/year for perimenopausal/postmenopausal women for AVG IMT; $p = 0.049$). Additionally, among the 160 perimenopausal/postmenopausal women, the intervention slowed IMT progression (0.008 mm/year for the control group vs. 0.004 mm/year for the intervention group for AVG IMT; $p = 0.02$). Similar results were found for the CCA and bulb segments.

**CONCLUSIONS** These data demonstrate that the menopause transition is associated with accelerated subclinical atherosclerosis progression and that a diet/exercise intervention slows menopause-related atherosclerosis progression. (J Am Coll Cardiol 2004;44:579–85) © 2004 by the American College of Cardiology Foundation

Subclinical atherosclerosis has been linked to higher rates of coronary heart disease (1), myocardial infarction (1), and stroke (2), and is considered a precursor to clinical cardiovascular events. Cross-sectionally, the menopause transition has been associated with subclinical disease levels, measured by both intima-media thickening (IMT) of the carotid arteries and by arterial distensibility (3–6). Whether the menopause transition is also associated with the progression of subclinical disease has not been established.

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During the menopause transition, low-density lipoprotein cholesterol (LDL-C) levels have been shown to increase, and high-density lipoprotein cholesterol (HDL-C) levels have been shown to decrease (7). Increased physical activity in mid-life has been shown to protect against these adverse lipid changes (8). Studies of mid-life have also documented substantial weight gain during this period, which has been associated with adverse changes in coronary heart disease risk factors (9). The Women's Healthy Lifestyle Project (WHLP) clinical trial was initiated to determine the efficacy of a dietary and physical activity intervention in preventing the weight gain and abnormal lipid profiles that occur at the time of menopause. By the end of the initial six-month intensive intervention period, the diet/activity intervention group achieved significant reductions in total cholesterol, triglycerides, weight, waist-to-hip ratio, systolic blood pressure (BP), diastolic BP, and serum glucose levels, and significant increases in physical activity (10). The intervention group maintained significantly lower weight, waist circumference, LDL-C, triglycerides, and glucose at the end of the 54-month trial (11).

Repeated IMT measures within the WHLP trial in combination with the success of the WHLP diet/activity intervention on lipid profiles and weight gain provided us with the opportunity to assess the following questions: was

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**Abbreviations and Acronyms**

ARIC = Atherosclerosis Risk In Communities study
BMI = body mass index
BP = blood pressure
CCA = common carotid artery
HDL-C = high-density lipoprotein cholesterol
ICA = internal carotid artery
IMT = intima-media thickness
LDL-C = low-density lipoprotein cholesterol
WHLP = Women's Healthy Lifestyle Project

progression of carotid atherosclerosis observable in these middle-aged women over the course of a four-year period, and if so, was progression related to menopause status or a lifestyle intervention?

## METHODS

**Study population.** From 1991 to 1994, 535 women age 44 to 50 years (92% Caucasian) were randomly assigned to a lifestyle-intervention group (n = 260) or to an assessment-only control group (n = 275). Eligible women were required to be premenopausal (defined as <3 months of amenorrhea in the 6 months before the telephone screening interview) and to have normal to high-normal ranges of diastolic BP, body mass index (BMI), fasting glucose, and cholesterol levels. Exclusion criteria included hormone therapy and current use of anti-hypertensive, lipid-lowering, insulin, thyroid, or psychotropic medications. The aim of the intervention was to reduce total dietary and saturated fat and cholesterol, prevent weight gain, and increase physical activity levels. Specific goals of the lifestyle intervention were a reduction of dietary fat to 25% of total fat, 7% of saturated fat, and 100 mg of cholesterol; a reduction in caloric intake to 1,300 kcal/day; and an increase in leisure-time physical activity to 1,000 to 1,500 kcal/week of energy expenditure. Participants who were randomized to the intervention program attended 15 group meetings held during the course of 20 weeks. Sessions were led by trained nutritional and behavioral interventionalists and were held weekly for 10 weeks, then biweekly for the remaining 10 weeks. After this intensive intervention, participants entered the maintenance phase of the program. Both the intervention and the control groups received clinical assessments at 6, 18, 30, 42, and 54 months after their date of randomization. Beginning in 1994, all of the women were invited to complete a carotid ultrasound scan. A total of 453 women were enrolled in the carotid study (response rate, 85%). The study was approved by the Institutional Review Board at the University of Pittsburgh, and all participants provided written informed consent.

**Clinical measures.** Clinical measures were assessed at study baseline and at each follow-up visit and included height, body weight, waist circumference, hip circumference, BP measures, and a fasting blood draw. The BPs were measured twice using a standard mercury sphygmomanometer after 5 min of rest. Total cholesterol, HDL-C, LDL-C, triglycerides, and glucose were determined using standard laboratory procedures. Fasting serum insulin was measured via radioimmunoassay. The BMI was calculated by dividing the participant's weight in kilograms by the square of her height in meters. Smoking status (current, former, never) and history of hysterectomy and hormone therapy use were assessed via questionnaire. Daily kilocalories expended through physical activity were also assessed via questionnaire (12).

Although hormone use was an exclusion criterion at baseline, women were permitted to begin hormone use after their baseline visit. Menopause status and hormone therapy use initiated after baseline were assessed at the time of the close of the intervention (54 months). One hundred and ten women initiated hormone use between baseline and the 54-month follow-up visit. Perimenopausal status was defined as skipping a bleeding cycle or taking hormone therapy for 3 to 11 cycles in the last year, and postmenopausal defined as skipping or taking hormone therapy for 12 or more consecutive cycles. Women who had undergone a hysterectomy were categorized as postmenopausal. Because of the low number of perimenopausal women, menopause status was collapsed into a dichotomous variable for analyses: premenopausal versus perimenopausal/postmenopausal.

**Carotid ultrasound.** Initial carotid scans were performed on 453 women an average of 2.7 years (range, 0.7 to 7.6 years) from the baseline WHLP examination. Second scans were performed on 357 women an average of 3.9 years (range, 0.8 to 6.9 years) after the initial scan. The American Heart Association grant that funded this study allowed for a third scan to be performed on approximately 100 women. Therefore, the first 113 women who underwent a second scan came in for a third scan an average of 2.5 years (range, 1 to 3.4 years) after the second scan.

Detailed B-mode images of the right and left common carotid artery (CCA), carotid bifurcation, and the first 1.5 cm of the internal carotid artery (ICA) were obtained at each ultrasound visit using a Toshiba SSA-270A scanner (Toshiba America Inc., New York, New York) equipped with a 5-MHz linear array imaging probe. To measure the average IMT of each segment, lines were electronically drawn along 1-cm segments of the lumen-intima interface and the media-adventitia interface of the near and far walls of the distal CCA and along the far walls of the carotid bulb and ICA. The average of these was recorded for each location. The mean of all average readings across the eight locations (four on each side) was calculated.

To assess the reproducibility of ultrasound measures, 15 participants had carotid scans performed by two different sonographers on two occasions approximately two weeks apart, and each scan was read by two readers. When accounting for all sources of measurement variation, the intraclass correlation for average IMT was 0.88. The average absolute difference in IMT between sonographers was 0.04 mm and between readers was 0.03 mm. These values

**Table 1.** Intervention and Control Group Characteristics at First Ultrasound Scan

| Variable | Intervention Group (n = 166) | Control Group (n = 188) | p Value |
|---|---|---|---|
| Average IMT (mm) | 0.66 (0.51–0.92) | 0.67 (0.51–0.92) | 0.56 |
| CCA IMT (mm) | 0.69 (0.50–0.91) | 0.67 (0.51–0.91) | 0.70 |
| ICA IMT (mm) | 0.61 (0.43–0.93) | 0.61 (0.41–0.93) | 0.78 |
| Bulb IMT (mm) | 0.73 (0.47–1.41) | 0.71 (0.46–1.54) | 0.11 |
| Age (yrs) | 49.4 (46.3–54.0) | 49.0 (46.5–54.1) | 0.70 |
| Systolic blood pressure (mm Hg) | 105.0 (79.0–153.0) | 106.5 (83.0–151.0) | 0.42 |
| Diastolic blood pressure (mm Hg) | 69.0 (48.0–94.0) | 70.0 (52.0–98.0) | 0.99 |
| Total cholesterol (mg/dl) | 193.0 (138.0–286.0) | 197.0 (119.0–271.0) | 0.09 |
| HDL cholesterol (mg/dl) | 62.3 (36.4–103.0) | 63.3 (30.6–114.0) | 0.75 |
| LDL cholesterol (mg/dl) | 111.0 (60.0–170.0) | 115.0 (45.0–173.0) | 0.19 |
| Triglycerides (mg/dl) | 85.0 (26.0–337.0) | 80.0 (33.0–380.0) | 0.96 |
| Glucose (mg/dl) | 98.0 (84.0–116.0) | 98.0 (78.0–138.0) | 0.26 |
| Insulin ($\mu$U/ml) | 12.0 (3.0–37.0) | 12.0 (3.0–62.0) | 0.46 |
| Body weight (lbs) | 142.0 (110.0–211.0) | 146.0 (106.0–228.0) | 0.04 |
| Waist girth (cm) | 75.0 (62.0–101.5) | 76.0 (62.0–105.0) | 0.13 |
| BMI (kg/m$^2$) | 23.9 (18.3–33.9) | 25.1 (18.6–35.9) | 0.01 |
| Daily kilocalories of exercise | 1,294.0 (28.0–9065.0) | 974.0 (0–8876.0) | 0.003 |
| Reached perimenopause or postmenopause*† | 75 (45) | 85 (45) | 0.96 |
| Undergone hysterectomy* | 3 (1.8) | 9 (4.8) | 0.12 |
| Hormone user* | 22 (13.3) | 39 (20.9) | 0.06 |
| Current smoker* | 14 (8.4) | 20 (10.7) | 0.47 |

*Values are n (%). †By 54-month visit. Data are presented as mean (range).
BMI = body mass index; CCA = common carotid artery; HDL = high-density lipoprotein; ICA = internal carotid artery; IMT = intima-media thickness; LDL = low-density lipoprotein.

compare favorably with those published from other research laboratories (13,14).

**Statistical analyses.** Age adjustment was made using the age at the first ultrasound scan. Laboratory and anthropometric variables were taken from WHLP study baseline as well as from the follow-up visit closest to the first ultrasound scan (median time between scan and closest follow-up visit was 119 days).

All statistical analyses were performed using the SAS system for Windows, version 8.2 (SAS Institute, Cary, North Carolina), and statistical significance was defined as $p < 0.05$ unless otherwise defined. Wilcoxon rank sum tests were used to assess differences in median values between the intervention and control groups at the baseline visit and at the time of the first ultrasound scan. The chi-square statistic was used to test differences in categorical variables between intervention and control groups at baseline and the time of the first ultrasound scan.

To assess IMT progression, change scores for each woman were created from the first ultrasound visit to the second (value at the second scan minus value at the first scan, standardized by the time between scans) and from the second to the third (value at the third scan minus value at the second scan, standardized by the time between scans) for the 113 women who underwent three scans. To determine whether or not IMT progression was even observed during the follow-up interval, these change scores were averaged, and a one-sample student *t* test was performed to determine whether changes were significantly different from zero.

To assess associations between treatment group or menopause status and annual change, accounting for the correlation between repeated carotid change scores for those with two change scores, repeated measures linear modeling (SAS Proc Mixed, SAS Institute) was used. Repeated change score models were run for each IMT measure, adjusted for age and the applicable IMT value at the first scan. To formally test whether the effects of menopause were altered by the intervention, an interaction term between menopause status and treatment group was tested, and the threshold for its significance was set at $p < 0.10$. To formally test whether the effects of the intervention among perimenopausal or postmenopausal women were altered by hormone use, an interaction term between menopause status and hormone use was tested, and the threshold for its significance was set at $p < 0.10$.

## RESULTS

There were 353 women with non-missing IMT data who had at least one change score, and all analyses used this subset of women. At WHLP baseline, those who were randomized to the intervention group had a higher median triglyceride value than those randomized to the control group (86.4 vs. 78.6; $p = 0.005$). No other significant differences were found between the two groups at baseline. By the time of the first carotid scan, however, evidence of the intervention could be seen in lower body weight values, lower BMI, and higher daily kilocalories of exercise among the intervention group compared with the control group (Table 1). At the time of the first ultrasound scan, IMT values did not differ between the intervention and control groups for any of the four carotid segments (Table 1).

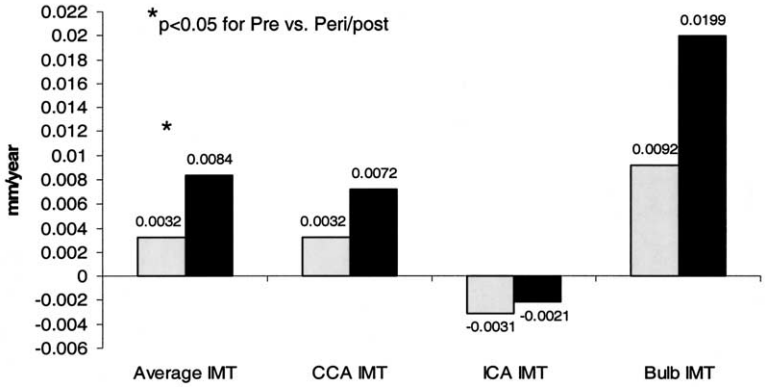


**Figure 1.** Mean annual intima-media thickness (IMT) changes (in mm/year) among the control group by menopausal status, adjusted for age and corresponding baseline intima-media thickness. **Gray bars** = premenopausal; **black bars** = perimenopausal/postmenopausal. CCA = common carotid artery; ICA = internal carotid artery.

Significant progression was observed for all of the carotid segments except for the ICA IMT. Mean annual changes for average IMT, CCA IMT, and bulb IMT were 0.007 mm/year, 0.008 mm/year, and 0.012 mm/year, respectively ($p < 0.01$ for all).

In order to see the natural effects of menopause without modification by the intervention, we evaluated the control group alone (Fig. 1). Among these women, a significant effect of menopause was demonstrated for average IMT; women who had undergone the transition to perimenopause or postmenopause had significantly larger annual changes in average IMT than women who remained premenopausal (Fig. 1). Although statistically significant for bulb IMT only, this pattern was present among all carotid segments (Fig. 2).

Among the whole sample, annual changes were not significantly different between the intervention and control groups (Table 2). To see the intervention effect clearly without modification by menopause, intervention analyses were stratified by menopause status. Among premenopausal women, no intervention effect was present for any carotid segment. However, among perimenopausal/postmenopausal women, the intervention group demonstrated significantly less progression than the control group (Fig. 2). Although statistically significant for average IMT and bulb IMT only, this pattern was present among all carotid segments (Fig. 2). The significant intervention effect among women who had undergone the transition to perimenopause and postmenopause indicates that the exercise and dietary intervention slowed the menopause-associated IMT progression. The differential intervention experience of premenopausal versus perimenopausal/postmenopausal women was confirmed by statistically significant treatment-by-menopause-status interaction terms for average IMT and bulb IMT in mixed modeling ($p = 0.060$ for average IMT and $p = 0.030$ for bulb IMT).

Hormone therapy use that was initiated after baseline was added to the above models and was not significantly associated with IMT progression, nor did it noticeably alter the results described above. Additionally, among perimenopausal/postmenopausal women, hormone use did not alter the effect of the intervention as tested by a hormone-by-treatment interaction term.

## DISCUSSION

Among these middle-aged women, our data document the measurable progression of average IMT, CCA IMT, and bulb IMT during a four-year follow-up period. These data also document the expected effect of menopause, with greater subclinical disease progression among women who had undergone the transition to perimenopause or postmenopause than among women who remained premenopausal. Importantly, these data also demonstrate that minimizing weight gain and adverse lipid changes through a diet and exercise intervention slowed the menopause-associated disease progression seen in the control group.

The results reported here for the perimenopausal/postmenopausal women are consistent with results for both males and females in the Atherosclerosis Risk In Communities (ARIC) study. Among ARIC study participants (age 45 to 64 years) the mean annual IMT progression was 0.0086 mm among women and 0.0091 mm among men (15). However, the IMT progression rates reported among premenopausal women of the current study are lower than both the males and females in the ARIC study, most likely owing to the higher age range of the ARIC study. There have been very few reports in the literature of the effects of

**Table 2.** Mean annual change in IMT by Intervention Status, Adjusted for Corresponding Baseline IMT

| Variable | Intervention | Control | p Value (Intervention vs. Control) |
|---|---|---|---|
| Average IMT (mm/yr) | 0.0051 | 0.0054 | 0.867 |
| CCA IMT (mm/yr) | 0.0057 | 0.0051 | 0.738 |
| ICA IMT (mm/yr) | −0.0013 | −0.0031 | 0.530 |
| Bulb IMT (mm/yr) | 0.0091 | 0.0131 | 0.280 |

CCA = common carotid artery; ICA = internal carotid artery; IMT = intima-media thickness

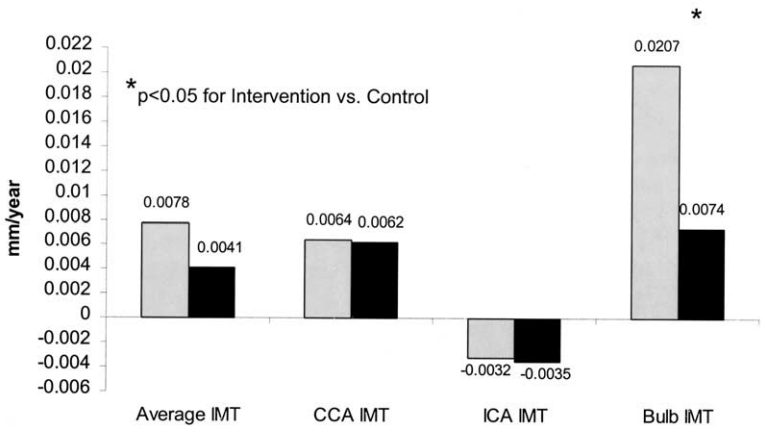


**Figure 2.** Mean annual intima-media thickness (IMT) changes (in mm/year) among perimenopausal/postmenopausal women by intervention group. **Gray bars** = control group; **black bars** = intervention group, adjusted for age and corresponding baseline IMT. CCA = common carotid artery; ICA = internal carotid artery.

a lifestyle intervention on IMT progression rates; most have been drug trials. In a nested observational study composed of nearly all males (91%), the Monitored Atherosclerosis Regression Study (MARS) reported that increases in dietary cholesterol, insoluble fiber, BMI, and smoking were all significant predictors of the annual IMT progression rate among participants in the placebo arm (16). Each 1-kg/m$^2$ increase in BMI associated with a 0.013 mm/year increase in IMT (16). In a Swedish population of middle-aged healthy males with moderately high cardiovascular risk factor values, an education program resulting in significant decreases in BP, lipids, and smoking was not found to be associated with the rate of IMT progression during the course of two years (17). Although slight, the existing literature may suggest that the effect of lifestyle intervention on IMT progression is specific to certain subgroups, such as those with existing atherosclerosis as found in the MARS or perimenopausal women as demonstrated in the current study. Future testing of lifestyle interventions in larger, representative populations is needed.

There are numerous ways in which the menopausal transition may affect the vasculature. First, the menopause transition is often accompanied by adverse lipid changes such as increased LDL-C and decreased HDL-C, whether assessed as a categorical status variable or in terms of continuous estrogen measures (7,18).

Second, the menopause transition is also associated with weight gain (19). Body weight has been linked to the development of insulin resistance, which has numerous vascular effects (20). The hyperinsulinemia that accompanies insulin resistance promotes sodium reabsorption (21,22), stimulation of the sympathetic nervous system (23,24), and vascular smooth muscle cell growth (25), whereas the glycemia accompanying insulin resistance can cause glycation of the proteins in the arterial wall, which have been associated with organ damage and atherosclerosis (26). Additionally, insulin bound to its receptor has potent vasodilator effects through endothelium-derived nitric oxide release (27), which may be compromised in the insulin-resistant state. Body weight may contribute to disease progression through inflammation (28,29). The presence of higher levels of circulating immune system cells may increase movement of these cells into the artery wall, leading to wall thickening and the development of atherosclerosis.

Finally, the menopause transition may be related to enhanced progression rates through direct effects of changing hormones on the vasculature. Estradiol has numerous vascular benefits, such as vasodilation and sympathetic nervous system effects, decreased collagen production leading to a decreased elastin/collagen ratio, and effects on smooth muscle cells (30–38). Progesterone, much like estrogen, also contributes to vasodilation and inhibition of smooth muscle growth (31). Androgens have vascular effects as well. Testosterone, although capable of arterial dilation directly, blocks the action of various dilation factors and promotes the action of certain vasoconstrictors (31).

In this study, the diet and exercise intervention slowed the menopause-associated IMT progression, with significantly less progression among the intervention group for women who had reached perimenopause or postmenopause. The intervention may have acted through its effects on lipid levels and weight gain. At the close of the intervention (54 months), those in the intervention group, compared with the control group, maintained significantly smaller positive changes from baseline in LDL-C (3.5 vs. 8.9 mg/dl), triglycerides (18.2 vs. 29.9 mg/dl), glucose (1.6 vs. 3.3 mg/dl), and body weight (−0.18 vs. 5.2 lbs) (11). In addition to smaller changes in overall body weight, the intervention group had significantly smaller changes in central adiposity, specifically −2.9 vs. 7 −0.46 cm change in waist circumference (11), which may promote subclinical disease progression through its associated insulin resistance (39,40). The intervention group also reported significantly greater amounts of physical activity than the control group. Physical activity has been associated with lower IMT values in cross-sectional studies (41,42) and may have direct effects

on the vasculature or may operate indirectly by eliciting favorable changes in risk factors. Finally, changes in the relative amounts of estrogens versus androgens occurring throughout the menopause transition may partially explain why the intervention was effective at decreasing menopause-associated IMT progression. These data suggest the perimenopause, as opposed to premenopause, as a critical time period for lifestyle intervention. An important question that these data cannot answer is whether the lifestyle intervention would have had the same effect if initiated late in postmenopause. Future research is needed among postmenopausal women to address this issue.

Although associations between subclinical disease progression, menopause, and the diet and exercise intervention were consistent for each carotid segment, statistical significance was not always achieved. Future research will need to confirm the effects of menopause, as well as those of diet and physical activity on IMT progression rates, in a larger sample of middle-aged women. Additionally, 92% of the women in the WHLP trial were Caucasian. Therefore, the results documented here may not be generalizable to other race/ethnic groups.

The changes in cardiovascular risk factors during the menopausal transition combined with hormonal effects on the vasculature may create an environment in which the vasculature is more prone to the development of atherosclerosis. Therefore, the perimenopause provides a critical time period during which to pursue risk-factor modification. The WHLP has demonstrated that a diet and exercise intervention successfully prevents the adverse risk-factor changes that accompany the menopause transition (10,11). The data reported here now document that this intervention slows menopause-related subclinical atherosclerosis progression, highlighting the beneficial effects of risk factor modification among perimenopausal women.

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