Changes in Cardiovascular Risk Factors During the Perimenopause and Postmenopause and Carotid Artery Atherosclerosis in Healthy Women

Karen A. Matthews, PhD; Lewis H. Kuller, MD, DrPH;
Kim Sutton-Tyrrell, DrPH; Yue-Fang Chang, PhD

Background and Purpose—The objectives of this study were to describe the changes in cardiovascular risk factors during the perimenopausal and early postmenopausal years and correlate those changes in risk factors with carotid intimal-medial thickness (IMT) and plaque index measured 5 to 8 years after menopause.

Methods—Participants were women (n=372) from Allegheny County, Pennsylvania, enrolled in the Healthy Women Study who had been postmenopausal for at least 5 years. Risk factor changes were measured during the perimenopause, ie, between the premenopausal and first year postmenopausal examinations, and during the early postmenopause, ie, between the first and fifth year postmenopausal examinations. Carotid ultrasound scans measured IMT and plaque at examinations 5 to 8 years after menopause among 314 of the women.

Results—Increases in LDL cholesterol and triglycerides and declines in HDL cholesterol were greater during perimenopause than postmenopause, whereas increases in blood pressure and fasting glucose levels were greater during postmenopause. Premenopausal systolic and pulse pressure, LDL and HDL cholesterol, triglycerides, and body mass index predicted IMT and plaque. Only the change in pulse pressure between premenopausal and first year postmenopausal examinations was related to both IMT and plaque.

Conclusions—Absolute risk for cardiovascular disease increases substantially in midlife, with a particularly adverse effect on lipid metabolism at the menopause. Premenopausal levels of risk factors are adequate to identify which women should be targeted for intervention. **(*Stroke*. 2001;32:1104-1111.)**

Key Words: blood pressure ■ body mass index ■ carotid artery diseases ■ menopause ■ women

Menopause is defined as the permanent cessation of menses due to depletion of viable follicles. Although estradiol levels are low after the initial cessation of menses, they continue to decline beyond the cessation of menses.[1] Furthermore, considerable variability in the level of estrogen in postmenopausal women occurs during the early postmenopausal years because of continued secretion of estradiol from the ovary and conversion of androstenedione to estrone in fat tissue.[2]

We have previously reported that in the Healthy Women Study, total and LDL cholesterol increase and HDL and HDL_2 cholesterol decline among premenopausal women who cease menstruating at least 1 year relative to age-matched premenopausal women who continue menstruating.[3] Blood pressure, insulin, glucose, weight, and waist circumference increase similarly among women who cease menstruating and women who continue menstruating. These conclusions are based on the first 65 women in the Healthy Women Study who became postmenopausal and are consistent with the results of other observational studies.[4,5] The first purpose of this article is to describe changes in cardiovascular risk factors among 372 healthy women from premenopause to 1 year after the cessation of menses, ie, during the perimenopause, and from 1 to 5 years after the menopause, ie, during the early postmenopause.

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Observational studies of natural menopause have not shown that an early age at menopause, an estimate of duration of exposure to low estrogen levels, is a risk factor for cardiovascular disease, independent of other cardiovascular risk factors, including socioeconomic status and smoking status.[6] Smoking and socioeconomic status are also predictors of age at menopause[7,8] as well as risk for cardiovascular disease, and therefore it is difficult to draw firm conclusions about the risk associated with menopause from these findings. The second objective of this article is to evaluate the association between risk factors before and after the meno-

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From the Department of Psychiatry, University of Pittsburgh School of Medicine (K.A.M.), and Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh (L.H.K., K.S.-T., Y.-F.C.) (Pa).

Reprint requests to Dr Karen A. Matthews, Department of Psychiatry, University of Pittsburgh School of Medicine, 3811 O'Hara St, Pittsburgh, PA 15213. E-mail matthewska@msx.upmc.edu

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pause and carotid artery atherosclerosis. We suggest that premenopausal risk factor levels are a stronger predictor of carotid artery atherosclerosis because they are a proxy for cumulative risk factor exposure during the premenopausal years, whereas the risk factor changes during the perimenopausal and early postmenopausal years have a shorter period of time for influence.

Subjects and Methods

Study Overview

In 1983–1984, we enrolled 541 premenopausal women in a study of changes in biological and behavioral characteristics of women as they experienced the menopause. They were contacted by letter sent to randomly selected women living within certain zip codes in Allegheny County, Pennsylvania, and subsequently were interviewed by telephone for eligibility. The following criteria was used: aged 42 to 50 years; menstrual bleeding within the last 3 months; no surgical menopause; diastolic blood pressure <100 mm Hg; and no medications known to influence biological risk factors under study, eg, estrogens, insulin, or lipid-lowering, thyroid, antihypertensive, and psychotropic medications. Sixty percent of eligible women volunteered. Most of the women were white because of the sampling procedure and selection criteria, eg, more blacks were excluded on the basis of their blood pressure levels and the fact that they were already postmenopausal. The University of Pittsburgh Institutional Review Board approved the project protocol, and all participants gave informed consent for their participation. Participant characteristics and recruitment procedures are described in detail elsewhere.[8]

All women completed a baseline examination and then reported their menstrual status on a monthly basis. When women reported that they had stopped menstruating and/or had taken hormone replacement therapy (HRT) for 12 months, they were considered postmenopausal and were reevaluated at that time and at 2, 5, and 8 years after menopause. Starting in September 1993, the carotid ultrasound measures were added to the protocol for women who were evaluated at 5 or 8 years after menopause.

The present report is based on the sample of 372 women (339 white, 31 black, and 2 from other ethnic groups) who completed examinations approximately 1 and 5 years after the menopause as of October 1997. The average age was 47.5 years at the premenopausal examination, with an average of 5.2 years (SE=0.12) elapsing until the first year postmenopausal examination and an additional average of 3.9 years (SE=0.02) elapsing until the fifth year postmenopausal examination. These women represented 78% of the women who were eligible for the fifth year postmenopausal examination. Of the 22% who did not participate, 17% of the potential participants had moved from the area, died, or withdrawn before the time of the fifth year postmenopausal examination, ie, only 5% declined participation.

Of the 372 women, 177 (including 22 nonwhites) never used HRT, 104 (including 6 nonwhites) received HRT at the first and fifth year postmenopausal examinations, 68 (including 3 nonwhites) used HRT at the fifth year postmenopausal examination only, and 23 (including 2 nonwhites) used HRT at the first year postmenopausal examination but did not continue hormone use at the fifth year postmenopausal examination. Starting in 1993, we added the carotid ultrasound protocol to the examination for women who were at least 5 years postmenopausal. Of the 372 women, 343 completed the ultrasound protocol; the 314 women who had complete data, including HRT use, constituted the basis of the analyses of carotid measures.

Protocol

After the telephone interview to determine eligibility and a home interview to record blood pressure levels, all women recruited were evaluated in the morning after fasting for 12 hours. This evaluation included collection of a blood sample for measuring serum lipoproteins and apolipoproteins; 2 measurements of blood pressure by the random zero–muddler method[9] by observers trained and certified according to the Multiple Risk Factor Intervention Trial protocol[10]; glucose loading (75 g) with blood sampling beforehand when fasting and 2 hours afterward; and a measurement of height and weight. Additionally, we used a questionnaire about health-related behaviors, including level of physical activity and alcohol consumption; a 24-hour food recall interview administered by a trained nutritionist with 3-dimensional models of food portions; and a self-report inventory containing standardized tests of personality and behavior. The postmenopausal examination was identical to the baseline examination, except that the glucose loading and 24-hour food recall interview were not readministered, and apolipoprotein and insulin assays were not completed. Additionally, the postmenopausal examination included a blood draw for determination of serum concentrations of follicle-stimulating hormone (FSH) and luteinizing hormone.

Laboratory Assays and Measurements

Levels of total serum cholesterol,[11] total HDL cholesterol,[12] HDL subfractions (HDL_2 and HDL_3),[13,14] and triglycerides[15] were measured by a lipid laboratory using the standards of the Centers for Disease Control. LDL cholesterol levels were estimated with the Friedewald equation.[16] Plasma glucose levels were determined by enzymatic assay (Yellow Springs glucose analyzer). Because of skewed distributions, the triglyceride and glucose values were log-transformed before analysis. The 2 measurements of blood pressure were averaged. The data for LDL cholesterol for 3 women were not included in the analyses because of triglyceride levels ≥4.52 mmol/L (400 mg/dL).

Ultrasound Protocol

A Toshiba SSA-270A scanner equipped with a 5-MHz linear array imaging probe was used. Sonographers scanned the right and left common carotid artery, the carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure intimal-medial thickness (IMT) and on any areas of focal plaque as well. The best images were taped and later digitized for scoring.

Trained readers measured the average IMT across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of IMT. A computerized reading program developed for the Cardiovascular Health Study[17] and modified in Pittsburgh was used. Readers also scored the ultrasound images for plaque in the proximal common artery, distal common artery, carotid bulb, internal carotid artery, and external carotid artery. Plaque was defined as a distinct area of hyperechogenicity and/or protrusion into the lumen of the vessel with at least 50% greater thickness than the surrounding area. For each segment, the degree of plaque was graded as follows: 0=no plaque; 1=1 small plaque <30% of vessel diameter; 2=1 medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; and 3=1 large plaque >50% of the vessel diameter or multiple plaques with at least 1 medium plaque. The grades were summed across right and left carotid arteries to create an overall measure of extent of focal plaque.

Reproducibility of IMT and the plaque index was assessed in 5 women who underwent 2 ultrasound examinations within 1 week. Each time, the women were scanned by 2 separate sonographers, and each scan was scored by 2 readers. When we accounted for both sonographer and reader variation, the intraclass correlation was 0.86 for IMT and 0.96 for the plaque index. The absolute difference in IMT between replicate scans was 0.03 mm.

Statistical Analysis

Paired *t* tests were used to determine whether the risk factors changed significantly from premenopausal to fifth year postmenopausal examinations. They were also used to determine whether the magnitude of the changes in the risk factors from premenopausal to

TABLE 1. Unadjusted Mean Premenopausal Risk Factor Levels and Changes in Risk Factor Levels at Follow-Up Examinations (n=372)

		Change at Follow-Up		
Characteristic	Premenopausal	Premenopausal to First Year Postmenopausal	First to Fifth Year Postmenopausal	Premenopausal to Fifth Year Postmenopausal
Systolic blood pressure, mm Hg	108.1 (0.6)	2.7 (0.6)	6.6* (0.8)	9.3 (0.8)
Pulse pressure, mm Hg	36.2 (0.4)	1.9 (0.6)	8.6* (0.7)	10.4 (0.7)
LDL cholesterol, mmol/L	2.78 (0.04)	0.47 (0.03)	0.06* (0.04)	0.53 (0.04)
HDL cholesterol, mmol/L	1.55 (0.02)	0.04 (0.01)	0.00 (0.01)	0.04 (0.01)
Triglycerides, mmol/L	0.92 (0.03)	0.23 (0.03)	0.11* (0.04)	0.33 (0.03)
Fasting glucose, mmol/L	4.82 (0.03)	−0.12 (0.05)	0.18* (0.05)	0.06 (0.06)
Body mass index, kg/m^2	24.6 (0.2)	1.3 (1.0)	0.6* (1.1)	1.9 (0.1)

Values in parentheses are SEM.

*Change scores differ in magnitude between premenopausal to first year postmenopausal and from first year to fifth year postmenopausal examinations adjusted for age and duration of follow-up; $P<0.05$.

first year postmenopausal examinations and from first to fifth year postmenopausal examinations differed, after adjustment for age and duration between the examinations. Because some women were using HRT at the first and/or fifth year postmenopausal examinations, the aforementioned paired *t* tests were conducted separately for ever and never users of HRT. Analyses were also conducted comparing the risk factor levels at baseline, first, and fifth year postmenopausal examinations of HRT users at first postmenopausal examination who began HRT before 6 months of amenorrhea and had no FSH data or had premenopausal levels of FSH versus those who began HRT after 6 months of amenorrhea or had postmenopausal levels of FSH. None of these group comparisons showed any significant results, and they are not presented below. Pearson correlations were used to determine the similarity in risk factors measured at premenopausal and at fifth year postmenopausal examinations. One-way ANOVA was used to examine the sociodemographic characteristics and baseline risk factors among women who differed in later use of HRT, after adjustment for age.

HRT users and nonusers at the first year postmenopausal examination had similar IMT ($P=0.37$) and plaque scores ($P=0.78$); HRT users and nonusers at the fifth year postmenopausal examination had similar IMT ($P=0.15$) and plaque scores ($P=0.14$). Therefore, risk factor changes between examinations were residualized for premenopausal risk factor levels, use of HRT, and age. Then 1-way ANOVAs with tests for linear trend were calculated between carotid IMT classified into quartiles of the sample distribution and premenopausal risk factor levels and residualized change scores. By *t* tests, we compared women with plaque scores of ≥2 versus those with 1 or 0 on premenopausal risk factors and residualized change scores. The plaque score of ≥2 is at the 71.2 percentile of the distribution of scores and represents focal plaque at least 30% or multiple small plaques. Multiple regression and multiple logistic regression identified the major premenopausal risk factors and change in risk factors that predicted IMT and plaque group, respectively. Two-tailed *P*-value of ≤0.05 was considered significant.

Results

Changes in Cardiovascular Risk Factors

At the premenopausal examination, the risk factor levels were relatively low in this sample of women because of study selection criteria (Table 1, column 1). The changes in risk factor levels were substantial across the follow-up period (column 4), with all risk factors, except HDL cholesterol, changing significantly from premenopausal to fifth year postmenopausal examinations. Twenty-eight percent of women (n=103) were current smokers at the premenopausal examination, whereas at the fifth year postmenopausal examination, 16.4% (n=61) were known to be smoking.

During the time from premenopausal to first year postmenopausal examinations, the changes in LDL cholesterol, triglycerides, and body mass index were larger than those between the first and fifth year postmenopausal examinations (columns 2 and 3). Changes in systolic blood pressure, pulse pressure, and fasting glucose were larger from the first to fifth year postmenopausal examinations than those from the premenopausal to first year postmenopausal examinations. Diastolic blood pressure did not change between initial and first postmenopausal examinations but declined significantly by the fifth year postmenopausal examination (mean=−2.0 mm Hg). The combination of an increase in systolic blood pressure and decline in diastolic blood pressure resulted in a substantial increase in pulse pressure across the study period.

Premenopausal risk factor levels did not vary according to subsequent HRT use in the postmenopausal years, except that women who never used HRT had higher systolic blood pressure and body mass index when premenopausal than women who took HRT after the menopause (Table 2, column 1). Ever and never users of HRT had similar changes in blood pressure and body mass index across the study period. However, never users of HRT showed a small decline in HDL cholesterol and an increase in fasting glucose levels, whereas the HRT users showed an increase in HDL cholesterol and no change in fasting glucose levels (column 4). Compared with ever users of HRT, never users of HRT had larger increases in LDL cholesterol and smaller increases in triglycerides from premenopausal to first year postmenopausal examinations and smaller declines in HDL cholesterol from first to fifth year postmenopausal examinations (Table 2, columns 2 and 3).

Correlations between risk factor levels measured at premenopausal and fifth year postmenopausal examinations were moderate to large for the entire group as well as for the HRT groups taken separately (Table 3). The magnitude of the correlations was significantly larger for triglycerides and body mass index for the never users of HRT than for the ever users of HRT. Nonetheless, the rank order of the women's

TABLE 2. Unadjusted Mean Premenopausal Risk Factor Levels and Changes in Risk Factor Levels at Follow-Up Examinations for Never Users (n=177) and Ever Users (n=195) of HRT

Characteristic	Premenopausal	Premenopausal to First Year Postmenopausal	First to Fifth Year Postmenopausal	Premenopausal to Fifth Year Postmenopausal
Systolic blood pressure, mm Hg				
HRT never user	109.8 (0.9)†	1.7 (0.9)	6.5 (1.2)*	8.1 (1.2)
HRT ever user	106.5 (0.7)	3.8 (0.9)	6.7 (0.9)*	10.5 (1.1)
Pulse pressure, mm Hg				
HRT never user	37.0 (0.7)	0.9 (0.8)	8.6 (1.1)*	9.5 (1.1)
HRT ever user	35.4 (0.5)	2.7 (0.7)	8.5 (0.8)*	11.2 (0.9)
LDL cholesterol, mmol/L				
HRT never user	2.81 (0.06)	0.57 (0.04)†	0.04 (0.05)*	0.60 (0.06)
HRT ever user	2.76 (0.05)	0.37 (0.05)	0.08 (0.05)*	0.47 (0.05)
HDL cholesterol, mmol/L				
HRT never user	1.52 (0.03)	0.02 (0.02)	−0.03 (0.02)†	−0.01 (0.02)†
HRT ever user	1.59 (0.02)	0.05 (0.02)	0.03 (0.02)	0.09 (0.02)
Triglycerides, mmol/L				
HRT never user	0.97 (0.05)	0.16 (0.04)†	0.13 (0.04)	0.30 (0.04)
HRT ever user	0.88 (0.03)	0.30 (0.05)	0.08 (0.06)*	0.37 (0.05)
Fasting glucose, mmol/L				
HRT never user	4.82 (0.04)	−0.07 (0.06)	0.22 (0.10)*	0.18 (0.10)†
HRT ever user	4.81 (0.04)	−0.17 (0.08)	0.14 (0.05)*	−0.04 (0.06)
Body mass index, kg/m^2				
HRT never user	25.4 (0.4)†	1.3 (0.2)	0.5 (0.2)*	1.8 (0.2)
HRT ever user	24.0 (0.3)	1.3 (0.1)	0.7 (0.1)*	1.9 (0.2)

Values in parentheses are SEM.

*Change scores differ in magnitude between premenopausal and first year postmenopausal and between first year and fifth year postmenopausal examinations, adjusted for age and duration (and HRT use for HRT users only); $P<0.05$.

†Change scores or premenopausal values differ in magnitude between never and ever users of HRT; $P<0.05$.

risk factors was fairly stable over the study period of nearly 13 years.

Risk Factor Change During the Menopause and Carotid Disease

As reported elsewhere in a subsample of the present group,[18] the higher the IMT quartile scores, the greater were the premenopausal levels of systolic blood pressure, pulse pressure, LDL cholesterol, triglycerides, fasting glucose, and body mass index and the lower were the premenopausal levels of HDL cholesterol (Table 4).

TABLE 3. Pearson Correlations of Risk Factor Levels at Premenopausal and Fifth Year Postmenopausal Examinations, Adjusted for Age, According to HRT Use

Characteristic	Never Used HRT	Ever User At First and/or Fifth Year Postmenopausal Examinations	All Participants
Systolic blood pressure	0.50	0.51	0.49
Pulse pressure	0.32	0.41	0.35
LDL cholesterol	0.63	0.63	0.63
HDL cholesterol	0.79	0.71	0.75
Triglycerides	0.69*	0.51	0.58
Fasting glucose	0.51	0.49	0.49
Body mass index	0.91*	0.86	0.89

*Never users and ever users of HRT; $P<0.05$ level.

Quartiles of IMT were associated with 3 residualized risk factor changes from premenopausal to fifth year postmenopausal examinations: systolic blood pressure, pulse pressure, and fasting glucose (Table 4). Analyses of change scores by time period showed that the systolic blood pressure and pulse pressure changes between the premenopausal and first year postmenopausal examinations were associated with IMT, whereas the fasting glucose change between the first and fifth year postmenopausal examinations was associated with IMT ($P<0.05$).

The multiple stepwise regression analyses in which hormone use at first and fifth year postmenopausal examinations and age were entered in the initial step, followed by any premenopausal risk factors that were significant in the second step, and by any risk factor change scores that were significant in the third step, showed that IMT (as a continuous variable) was predicted by premenopausal triglycerides level ($\beta=0.21$, $P<0.002$), premenopausal pulse pressure ($\beta=0.30$, $P<0.001$), and change in pulse pressure from premenopausal to fifth year postmenopausal examinations ($\beta=0.18$, $P<0.001$).

Relative to women with a plaque score of 0 or 1, women who had a plaque index of ≥2 had a more atherogenic risk

TABLE 4. Unadjusted Mean Levels of Cardiovascular Risk Factors at Premenopausal and Change at 5 Years Postmenopausal Among Women Classified into Quartiles of IMT Scores at 5 to 8 Years After Menopause

	Quartiles				
Risk Factor	1	2	3	4	*P* for Linear Trend*
Systolic blood pressure					
Premenopause	104.9 (1.2)	106.4 (1.1)	107.8 (1.2)	112.3 (1.4)	0.000
Change	6.4 (1.5)	7.0 (1.6)	9.2 (1.6)	10.0 (1.9)	0.008
Pulse					
Premenopause	34.3 (0.8)	34.7 (0.8)	35.6 (0.8)	39.4 (0.9)	0.000
Change	6.9 (1.2)	8.9 (1.3)	10.4 (1.3)	11.4 (1.4)	0.000
LDL cholesterol, mmol/L					
Premenopause	2.65 (0.09)	2.72 (0.08)	2.65 (0.07)	3.06 (0.10)	0.003
Change	0.52 (0.08)	0.45 (0.08)	0.68 (0.07)	0.43 (0.09)	0.49
HDL cholesterol, mmol/L					
Premenopause	1.63 (0.04)	1.64 (0.04)	1.50 (0.04)	1.46 (0.04)	0.001
Change	0.05 (0.03)	0.03 (0.03)	0.07 (0.03)	0.02 (0.03)	0.49
Triglycerides, mmol/L					
Premenopause	0.78 (0.04)	0.88 (0.06)	0.90 (0.05)	1.14 (0.08)	0.000
Change	0.35 (0.06)	0.42 (0.07)	0.31 (0.07)	0.28 (0.07)	0.56
Fasting glucose, mmol/L					
Premenopause	4.75 (0.07)	4.76 (0.06)	4.83 (0.06)	4.87 (0.06)	0.09
Change	−0.02 (0.09)	0.02 (0.06)	0.10 (0.09)	0.05 (0.13)	0.06
Body mass index					
Premenopause	23.6 (0.4)	24.2 (0.5)	24.9 (0.5)	25.2 (0.6)	0.015
Change	1.9 (0.3)	1.7 (0.2)	2.3 (0.3)	1.9 (0.3)	0.95

Values in parentheses are SEM.

*Linear trends for changes scores adjusted for premenopausal levels, age, use of HRT. Quartile values for IMT are 0.71 for the 25th, 0.76 for the 50th, and 0.83 for the 75th percentiles.

factor profile at their premenopausal examination, with greater systolic blood pressure, pulse pressure, LDL cholesterol, triglycerides, and body mass index and lower HDL cholesterol (Table 5). Women who had a plaque score of 0 or 1 tended to differ from those with a plaque score ≥2 in magnitude of changes in HDL cholesterol and pulse pressure from premenopausal to fifth year postmenopausal examinations, adjusted for premenopausal level, age, and use of HRT (Table 5). Those with a plaque score of 0 or 1 had larger changes in HDL cholesterol (means=0.06 versus 0.005; $P=0.02$) and smaller changes in pulse pressure (means=1.6 versus 2.2; $P=0.04$) between the premenopausal and first year postmenopausal examinations than those with plaque scores of ≥2. The changes in LDL cholesterol tended to be

TABLE 5. Unadjusted Mean Premenopausal Risk Factor Levels and Changes in Risk Factor Levels at Follow-Up Examinations According to Plaque Index Score 2 (n=86) vs 0, 1 (n=228)

	Premenopausal			Premenopausal to Fifth Year Postmenopausal		
Characteristic	PI<2	PI≥2	*P*	PI<2	PI≥2	*P*
Systolic blood pressure, mm Hg	106.9 (0.7)	110.9 (1.3)	0.006	8.3 (0.9)	8.3 (2.0)	0.49
Pulse pressure, mm Hg	35.1 (0.5)	38.4 (0.9)	0.002	9.3 (0.7)	10.4 (1.5)	0.06
LDL cholesterol, mmol/L	2.69 (0.05)	2.99 (0.09)	0.002	0.52 (0.05)	0.54 (0.09)	0.44
HDL cholesterol, mmol/L	1.58 (0.02)	1.49 (0.05)	0.09	0.06 (0.02)	−0.01 (0.03)	0.07
Triglycerides, mmol/L	0.86 (0.03)	1.11 (0.08)	0.002	0.37 (0.04)	0.25 (0.07)	0.35
Fasting glucose, mmol/L	4.77 (0.04)	4.91 (0.06)	0.20	0.01 (0.06)	0.11 (0.10)	0.20
Body mass index, kg/m^2	24.3 (0.3)	25.1 (0.5)	0.13	2.0 (0.2)	2.0 (0.3)	0.99

Values in parentheses are SEM. PI indicates plaque index.

$P<0.05$ for group differences adjusted for age for premenopausal levels and adjusted for age, premenopausal level, and use of HRT for change scores.

larger among those with more plaque during the perimenopausal transition as well (means=0.53 versus 0.43; $P<0.08$). No changes in risk factors during the early postmenopausal period predicted plaque group.

The stepwise logistic regression analysis showed that plaque group was predicted by premenopausal triglyceride level (odds ratio=2.62; $P<0.002$), HDL cholesterol change from premenopausal to first year postmenopausal examination (odds ratio=0.97; $P=0.05$), and triglyceride change from first to fifth year postmenopausal examination (odds ratio=0.99; $P=0.03$).

Discussion

The present study had 2 major objectives. First, it described the changes in risk factors for cardiovascular disease in healthy middle-aged women over an interval of time when women underwent the transition from being premenopausal to cessation of menses for at least 5 years. Second, it evaluated whether the magnitude of the changes in risk factors during the perimenopausal and early postmenopausal transition predicted carotid disease, above and beyond what was predicted by premenopausal risk factor levels.

Results showed that the overall changes in risk factors from premenopause to 5 years after menopause were substantial in healthy women in midlife, suggesting increasing absolute risk of atherosclerosis. However, the magnitude of the risk factor changes varied substantially between the perimenopausal and the early postmenopausal periods, ie, between the premenopausal and first year postmenopausal examinations versus the first and fifth year postmenopausal examinations. The changes in LDL cholesterol, triglycerides, and body mass index during the perimenopause were larger than those after the menopause. The changes in systolic blood pressure, pulse pressure, and fasting glucose were larger after the menopause. Variation in the magnitude of change is probably due to the differential determinants of risk factor change, with reduced estradiol levels, weight gain, and increased waist circumference important during the perimenopausal period, and with aging effects, such as increased vascular stiffness and increased proportion of body fat, important during the early postmenopause.

The changes in lipids varied across groups classified according to hormone use, with the largest increases in LDL cholesterol and a small decline in HDL cholesterol apparent among the never users of HRT. The effects of HRT use on lipid characteristics obtained in this observational study are by and large consistent with the findings of an early report based on 101 postmenopausal women from this sample[3] and with those of clinical trials, including the Postmenopausal Estrogen/Progestin Interventions trial.[19] Even so, it is noteworthy that there is a significant increase in LDL cholesterol even among users of HRT at both postmenopausal examinations, with LDL cholesterol increasing 0.25 mmol/L (9.6 mg/dL) between the premenopausal and first year menopausal examinations and increasing another 0.11 mmol/L (4.1 mg/dL) between the first and fifth year postmenopausal examinations.

At least 5 years after the menopause, a substantial number of women had measurable plaque, with almost 25% having a plaque score of ≥2. As reported elsewhere in a subsample of the study group,[18] women with elevated plaque or IMT scores had an atherogenic risk factor profile when they were premenopausal, including elevated systolic blood pressure, pulse pressure, LDL cholesterol, triglycerides, and body mass index and low HDL cholesterol.

Only the change in pulse pressure during the perimenopause was a consistent predictor of both IMT and plaque groups, beyond the premenopausal level of pulse pressure, and with adjustment for age and use of HRT. The importance of pulse pressure change before and during the menopausal transition in predicting future IMT is noteworthy. An increase in pulse pressure accompanies the structural changes that occur with age, including fragmentation and degeneration of elastin, increases in collagen, and a thickening of the arterial wall.[20] Arterial stiffening occurs at different rates for different individuals and may be viewed as a process of aging of the vascular system that is accelerated during a period of rapid estrogen decline.

Why might premenopausal levels of risk factors be excellent predictors of postmenopausal carotid IMT and plaque? The associations between risk factors before and after the menopause indicate substantial stability in relative rank of women's risk, ie, the women's absolute risk during the menopausal transition increases in a fairly uniform fashion. The premenopausal levels of risk factors may be a good measure of risk factor levels during the premenopausal years before women entered into the study. There is an incubation period for the development of carotid atherosclerosis. Perhaps the length of follow-up of 4 years during the early postmenopausal years in the present study is too brief for the effects of the substantial change in risk factors to appear on IMT or plaque measure. Perhaps menopausal risk factor changes will be stronger predictors of carotid disease when the women are aged 60 to 70 years. In any event, our findings indicate that high-risk women can be identified in the premenopausal years and that prevention strategies should not await the substantial risk factor changes that occur during and after the menopausal transition.

In conclusion, our results indicate that, in midlife, substantial increases in absolute risk of cardiovascular disease occur as women experience the cessation of menses and beyond. The changes in lipids are larger between the premenopausal and first postmenopausal years than between the first and fifth postmenopausal years. Premenopausal levels of risk factors are strong determinants of carotid IMT and plaque measured 5 to 8 years after the menopause, but only the change in pulse pressure during the perimenopausal years is related to subsequent carotid disease. Risk factor modification aimed at middle-aged premenopausal women is worthwhile to prevent the development of atherosclerosis in the postmenopausal years.

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Editorial Comment

Premenopausal Risk Continuum for Carotid Atherosclerosis After Menopause

In the preceding article, Matthews and colleagues report on the shifting profile of important cardiovascular risk factors during the transition into early menopause in healthy women and examine the relationship of these factors to carotid artery atherosclerosis. The authors describe the association of carotid intima-media thickness (IMT) and carotid artery plaque measured between 5 and 8 years after menopause to changes in cardiovascular risk factors during the perimenopause and early postmenopausal epoch in 372 women. Adverse variations in blood pressure, pulse pressure, lipid metabolism, fasting blood glucose, and body mass index were seen by the fifth postmenopausal year. Of these, only a change in pulse pressure in the perimenopausal years were associated with the development of atherosclerosis, but this may simply reflect the relatively short follow-up time. Premenopausal levels of systolic and pulse pressure, LDL and HDL cholesterol, triglycerides, and body mass index all predicted IMT and carotid plaque and showed a dose response when women were classified into quartiles of IMT at 5 to 8 years after menopause. As the authors note, this suggests middle-aged premenopausal women can be targeted for primary intervention to prevent the development of atherosclerosis. Perhaps the most interesting aspect of this work is that absolute levels of all of these premenopausal predictors of carotid atherosclerosis, while significantly elevated compared with the women without atherosclerosis, were in the normal ranges.

Cardiovascular risk appears to follow a continuum for many risk factors rather than respecting absolute cutoff values.[1] Although the most recent recommendations suggest that lipid screening programs are not cost effective for asymptomatic premenopausal women,[2] the work by Matthews and colleagues supports the notion of a cardiovascular risk continuum and suggests that the real benefit of asymptomatic screening may be to intervene in a process that will take many years to evolve into a clinical event. Recent work in the risk associated with elevated blood pressure has clearly shown that although a normal range is accepted, lower may be better.[3] The interplay of cardiovascular risk factors may also be important in the development of atherosclerosis. There is, for example, evidence that carotid artery IMT is more strongly related to LDL in the setting of elevated SBP, thus supporting the "response to injury" hypothesis of atherosclerosis.[4]

Given, as Matthews and colleagues note, that there are substantial increases in the absolute risk of cardiovascular disease associated with the transition into menopause, does hormone replacement therapy (HRT) alter that risk? There is strong evidence from large epidemiological studies that HRT are cardioprotective,[5] although the beneficial effects decrease with age[6] and advancing coronary disease.[7] Matthews and colleagues stratify healthy young women by HRT use and demonstrate that there is a beneficial effect on a number of individual risk factors. The correlation between risk factor levels measured at the beginning and end of their study period remained strong for women using HRT, as it did for the entire group. The association between HRT use and less atherosclerotic changes of the carotid, as has been suggested by data from a more elderly population,[8] was not directly assessed. Nor was this study designed to evaluate the differential effect on individual risk factors of various formulations of HRT, which have in other studies been shown to have varying affects on lipid metabolism[9] and prothrombotic parameters.[10] These remain important concerns, given the fact that there is no compelling evidence that HRT protects against stroke risk[11,12] and may even be deleterious.[12,13]

The authors should be congratulated for this meaningful contribution to the literature of gender-based differences in cardiovascular risk. Their work highlights the importance of reestablishing normal ranges for blood pressure and lipids for premenopausal women with a risk continuum in mind and investigating the benefits of cholesterol-lowering statins, aggressive blood pressure control, and HRT use for primary stroke prevention in women.

Gretchen E. Tietjen, MD, *Guest Editor*
Department of Neurology
Medical College of Ohio
Toledo, Ohio

Robin L. Brey, MD, *Guest Editor*
Division of Neurology
University of Texas Health Sciences Center
San Antonio, Texas

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Karen A. Matthews, Lewis H. Kuller, Kim Sutton-Tyrrell and Yue-Fang Chang

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