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Premenopausal Risk Factors for Coronary and Aortic Calcification: A 20-year Follow-up in the Healthy Women Study

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Abstract

Objective—It is important to understand the early development of subclinical cardiovascular disease (CVD) in women to prevent costly morbidity and mortality associated with CVD events.

Methods—363 women enrolled in the Healthy Women Study, Allegheny County PA had electron beam tomography measures of coronary (CaC) and aortic (AC) calcification on average 14.6 years after study entry in 1983; 267 had a second EBT 6.4 years later, by 2006. Risk factors were assessed when women were premenopausal and five years after the menopause.

Results—Step-wise logistic regression analyses showed that the independent premenopausal predictors of CaC ≥ 100 14.6 years later were low density lipoprotein cholesterol, OR= 1.15 (1.03-1.29 for 10 mg/dl) and current smoker, OR= 2.72, 1.29 – 5.71. The same premenopausal risk factors were predictors of AC ≥ 500 , in addition to premenopausal systolic blood pressure (SBP). Similar results were obtained for predicting calcification 20.6 years later. Postmenopausal risk factors measured 5 years prior to the initial scans were unrelated to CaC and AC, after the significant premenopausal risk factors were taken into account, except for postmenopausal SBP being related to AC.

Conclusion—Premenopausal risk factors are strong predictors of postmenopausal CaC and AC. Clinical trials should test if reduction of premenopausal levels of risk factors reduces the risk of early calcification.

Keywords

Women; coronary calcification; risk factors; menopause

Introduction

The development of reliable tools to measure extent of subclinical atherosclerosis, such as electron beam tomography (EBT), has provided new opportunities to study the relationship between risk factors early in life and later subclinical CVD (Budoff et al, 2006). EBT identifies

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and measures coronary artery calcification (CaC) as a gauge of atherosclerotic burden. CaC is related to extent of coronary atherosclerosis and predicts subsequent clinical coronary heart disease (CHD; Arad et al, 2005; Raggi et al, 2004; Taylor et al, 2005). Aortic calcification (AC) can also be evaluated by EBT and has been related to cardiovascular disease (Reaven and Sacks, 2005). CaC is greater among men than women and increases with age (Hoff et al, 2001), but AC is similar or more prevalent in women than in men (Danielson et al. 1996; McGill et al, 2000).

Several longitudinal studies of healthy populations report that cardiovascular risk factors measured in persons in young and mid-adulthood are related to later CaC. (Bild et al. 2001; Daviglus et al. 2004; Mahoney et al. 1998). Here we report cardiovascular risk factors measured prior to and after the menopause as predictors of CaC and AC measured 14.6 to 20.4 years later in 363 women enrolled in the Healthy Women Study. It extends our prior report by examining the associations in a sample twice as large as reported previously (Kuller et al. 1999) and over a longer follow-up period with multiple follow-ups. We hypothesized that cardiovascular risk factors measured in mid-life when women were premenopausal would be strong predictors of later CaC and AC. Second, we expected that postmenopausal risk factors, although measured closer in time to assessment of CaC and AC and after menopause-induced changes in risk factors (Matthews et al, 1989 a; Lindquist, 1982) would have little predictive value beyond that offered by premenopausal risk factors. The rationale for this hypothesis was related to the relative stability of risk factor trajectories over time and the shorter incubation period for postmenopausal risk factors to have unique effects (Matthews et al, 2001). If these hypotheses are confirmed, they reinforce the importance of prevention of atherosclerosis beginning among women in the premenopausal years.

Methods

Participants

The 363 participants were from the ongoing Healthy Women Study. In 1983-1984, women between the ages of 42 and 50 who had driver's licenses in Allegheny County, PA were interviewed about their eligibility for the study and 90% agreed to the interview. Eligibility criteria included: menstrual bleeding within the past 3 months, no surgical menopause, DBP <100 mmHg, and not using lipid-lowering, anti-hypertensive, psychotropic medications, thyroid hormone, estrogens or insulin. 60% of eligible women or 541 women agreed to join the Healthy Women Study. Details of recruitment and sample characteristics are available elsewhere (Matthews et al, 1989 b).

Assessment of cardiovascular risk factors and psychosocial characteristics was completed at baseline. When a woman reported amenorrhea and/or the initiation of hormone therapy (HT) for 12 successive months, she had a follow-up evaluation, which was repeated at approximately 2, 5, and 8 years after the menopause. Starting in 1997, women who remained in the Pittsburgh area and were at least 5 years post-menopause were invited to have an EBT of their coronary arteries and aorta. As of August 31, 2006, 363 women had completed a first scan; 267 women had a second scan on average 6.4 years later. The University of Pittsburgh Institutional Review Board approved the project, and all participants provided written informed consent.

Of the original 541 women enrolled in the Healthy Women Study, 21 refused the EBT protocol, 13 were deceased, 56 had dropped out prior to EBT being instituted, 68 moved out of the area, 1 was lost to follow-up, and 19 remained to be scheduled. Comparisons of the 363 participants vs. the 178 women who did not participate in the EBT protocol showed the participants were more often Caucasian and married and had somewhat lower blood pressure, fasting insulin, but were similar in age, educational attainment, weight, and lipids to the nonparticipants. Of those with first scans, 17 refused the second scan, 11 moved out of the area, 2 died, and 2

dropped out of the study; most of the remainder without a second scan have less than 6 years between scans and are still being followed (N=23). Comparison of those with a second scan vs. those with the first scan only showed no differences in any of the cardiovascular risk factors at baseline, all p s $\geq .12$.

Assessment of Cardiovascular Risk Factors

Levels of total serum cholesterol, HDL-C, and triglycerides were determined by conventional enzymatic methods from fasting (12 hour) blood samples (Gidez et al, 1982; Warnick and Albers, 1978; Bucolo and David, 1983; Allain et al, 1974). LDL-C was estimated by the Friedewald equation (Friedewald et al, 1982). Apolipoprotein B (ApoB) was measured by electroimmunoassay and only at baseline examination. Plasma fasting glucose levels were determined by enzymatic assay (Yellow Springs glucose analyzer). Plasma insulin concentrations were measured by radioimmunoassay but fewer samples were measured due to fiscal constraints in follow-up years so only baseline associations are reported below. Cigarette smoking was defined by self-report of current smoking. Measurements of height and weight were converted to BMI (weight in kilograms/height in meters squared). Waist circumference was measured after the baseline evaluation. Blood pressure was measured by random zero muddler method (Dischinger and DuChene, 1986; Garrow 1963).

Assessment of Calcification

An EBT-trained technician used an Imatron C150 scanner (GE-Imatron, South San Francisco, CA) and its densitometric program to assess the extent of calcification in the coronary arteries and aorta. During coronary scanning, 30 to 40 contiguous 3-mm-thick transverse images were obtained from the level of the aortic root to the apex of the heart during maximal breathholding by using electrocardiogram triggering so that each 100-millisecond exposure was obtained during the same phase of the cardiac cycle, 80% of the R to R interval. During a second pass, 6 mm continuous images of the aorta (30-millisecond exposure) were obtained from the aortic arch to the iliac bifurcation. From these images, we derived Agatston calcium scores (Agatston et al, 1996; Agatston et al, 1990), based on 3 or more contiguous pixels greater than 130 Hounsfield Units (HU) units being detected. We reported high EBT scan-to-scan reproducibility of coronary and aortic calcium scores (intraclass correlation = 0.99), with extremely small measurement error due to reader in 80 women with repeated readings (Sutton-Tyrrell et al; 2001).

Methods of Analysis

Significance was defined as a p -value ≤ 0.05 (two-tailed test). Pearson correlation coefficients evaluated the associations between risk factors at the examinations and Spearman rho coefficients evaluated the associations between CaC and AC. Because the calcification scores were highly skewed, especially CaC, women were divided into groups based on the distributions of CaC and AC scores into clinically meaningful categories. The group differences in age-adjusted risk factors were evaluated by analyses of variance (ANOVA) with tests for linear trend. Multivariable analyses using step-wise logistic regression (after forcing in age) evaluated the independent predictors of CaC > 100 and AC > 500. SAS v. 8.2 was used for analysis.

Results

Sample Characteristics at Baseline Premenopausal and Fifth Year Postmenopausal Examinations

The 363 participants who participated in the EBT protocol 14.6 years later on average, standard deviation [(SD)=1.4, range 12.5 – 20.3] were healthy at study entry because of the exclusionary

criteria. Most were white (93.4%) and better educated (50.4% college graduates) because the exclusionary criteria (e.g. DBP > 100, diabetes, no hysterectomy) preferentially excluding nonwhites. Participants were middle-aged and on average had lipids, blood pressure, and weight within the usual range considered to be healthy (Table 1; left column).

The majority or 53% had no CaC at their first EBT evaluation with 49 or 13.5% having scores > 100. CaC range of scores was 0 to 1175. This distribution is similar to other reports of asymptomatic women ages 60-64, in which the scores for CaC at the 25, 50, 75, and 90 percentile were 0, 3, 57, 193 respectively (Hoff et al. 2001). The second EBT evaluation of 267 women showed 100 or 37.5 % had no CaC and 63 or 23.6 % had scores >100; range of scores was 0 to 2707. The second EBT evaluation occurred 20.6 years (SD = 0.8; range 19.0-22.7 years) after study entry. Fewer women (86 or 24.5%) had no AC at the first EBT evaluation and even fewer women (30 or 11.4%) had none at the second EBT evaluation. The associations between CaC and AC were $r = 0.42$ ($p < 0.0001$) and $r = 0.43$ ($p < 0.0001$) at the first and second EBT evaluation, respectively.

Among the 363 women, having a heart attack was strongly related to the initial CaC: the rates of heart attack were 0 among the 191 women with 0 CaC, 3.5% among the 47 women with scores of 1-10; 9.2% among the 65 women with scores of 11-100; and 12.2% among the 49 women with score > 100, $p = .0001$.

Between the premenopausal baseline and the fifth year postmenopausal evaluations, LDL-C, triglycerides, insulin, and SBP increased substantially; DBP did not change (Table 1). Risk factor levels measured at baseline and fifth year postmenopausal evaluation were quite similar in relative rank. 98 women or 27% reported smoking at baseline and 47 or 15% reported smoking at the fifth year postmenopausal evaluation; only 3 nonsmokers at baseline reported smoking at the fifth year postmenopausal evaluation. Higher baseline levels of risk factors were related to smaller increases between baseline and fifth year postmenopause evaluations in LDL-C, HDL-C, SBP, and glucose, likely due to regression to the mean.

Premenopausal (Baseline) Predictors of Later Calcification

Baseline premenopausal levels of LDL-C, ApoB, HDL-C, triglycerides, SBP, insulin, and smoking status were associated with extent of CaC 14.6 years later (Table 2). Only glucose level was unrelated to CaC. The same premenopausal baseline risk factors were associated with CaC measured 20 years after study entry (data not shown), except that baseline insulin, $p = .29$, and glucose levels, $p = .13$ became nonsignificant.

To illustrate the pattern of associations across multiple risk factors, we examined the associations between tertiles of baseline HDL-C and LDL-C among smokers and nonsmokers with CaC at the first EBT (Table 3). Among nonsmoking women in the highest tertile of HDL-C and lowest tertile of LDL-C, 70.2% were in 0 CaC group and only 4.3% in the >100 CaC group. In contrast, among smokers in the lowest tertile of HDL-C and the highest tertile of LDL-C, only 28.6% were in the 0 CaC group and 33.3% in the >100 group. The same overall pattern was also apparent when women were classified into tertiles of ApoB scores in place of LDL-C.

As was the case for associations with CaC, baseline premenopausal levels of LDL-C, ApoB, HDL-C, triglycerides, SBP, DBP, insulin, and smoking status were associated with extent of AC 14.6 years later (Table 4). Glucose level was unrelated to AC and BMI only tended to be related to AC. The same premenopausal risk factors were associated with AC measured 20.6 years after study entry (data not shown). Baseline insulin levels remained a significant predictor of AC, $p = .02$.

Postmenopausal Risk Factors as a Predictor of Later Calcification

The number of women in the analysis of postmenopausal risk factors was 308 (not 350) because some women did not attend the fifth postmenopausal clinic visit, even though they attended the EBT clinic evaluation as well as postmenopausal clinic visits in other years. HDL-C, triglycerides, and smoking status measured at the fifth year postmenopausal examination on average 5 years (SD=2.2; 0 – 11.7 years) prior to the first EBT were related linearly to CaC groups based on the first EBT (Table 5). Because almost 50% of women were on HT at the time of the fifth year postmenopausal clinic, the analyses were repeated adjusting for hormone status, as well as use of statins (N=14), and antihypertensive (N=26) and diabetes medications (N=4). The relationships of risk factors and CaC groups were virtually identical to those shown in Table 4, although LDL-C was marginally associated, $p = .06$. HT use at the fifth postmenopausal evaluation was unrelated to CaC groups, $p = .35$; 88 women had used HT at both the first and fifth year postmenopausal evaluations.

LDL-C, HDL-C, SBP, and smoking status at the fifth year postmenopausal evaluation predicted the linear association with AC groups at the first EBT (Table 6). Adjustments for age, and hormone and medication use did not alter the results.

Premenopausal and Postmenopausal Risk Factors as Predictors of Later Calcification

Premenopausal (baseline) LDL-C and smoking status were independent predictors of having CaC ≥ 100 14.6 years later in multivariate analyses in the sample of 363 women. After baseline levels of age, LDL-C and smoking status, and fifth year postmenopausal examination reports of HT use and medications for blood pressure, lipid lowering, and diabetes were entered into the model, no risk factor measured at the fifth year postmenopausal evaluation was a statistically significant predictor of CaC ≥ 100 at 14.6 years or 20.6 years after study entry in the 293 with both premenopausal and postmenopausal risk factors (Table 7).

Premenopausal LDL-C, SBP, and smoking status were independent predictors of having AC ≥ 500 14.6 years later in the sample of 363 women. After baseline levels of LDL-C, SBP, and smoking status were entered into the model, along with use of HT, antihypertensive medications, and lipid-lowering and diabetic agents at the fifth year postmenopausal evaluation, SBP measured at the fifth year postmenopausal examination was also a significant predictor in the sample of women with both premenopausal and postmenopausal risk factors (Table 7).

Risk factor changes between examinations were unrelated to either CaC or AC 14.6 years after baseline, except for one risk factor. Changes in glucose were larger in the higher CaC groups: mean = 3.76 for CaC ≥ 100 ; mean = 3.10 for CaC 11-100; mean = .58 for CaC 1-10; and mean = -0.95 for CaC of 0.

Discussion

Our findings show that premenopausal levels of risk factors are strong predictors of the extent of CaC and AC 14.6 – 20.6 years later. Multivariate analyses showed that LDL-C, triglycerides, smoking status, and SBP were independent predictors of calcification. Our findings also demonstrate that favorable levels of risk factors during the premenopausal years may be particularly protective: 70.2% of nonsmokers who had HDL-C in the highest tertile and LDL-C in the lowest tertile of the distribution of scores had no detectable CaC after 14.6 years. Our findings parallel cross-sectional associations between a favorable risk factor profile and CaC in the Multi-Ethnic Study of Atherosclerosis (MESA) (Davignus et al, 2005); longitudinal associations between a favorable risk factor profile and long-term risk of CVD and all-cause mortality in the Chicago Heart Association Detection Project (Davignus et al, 2004 b); and

longitudinal associations between risk factors in young adulthood and CaC 20 years later, with concurrent risk factors being less powerful predictors of CaC (Carr et al, 2007).

Our findings show substantial changes in lipids and blood pressure occurred between premenopause and five years after the menopause. Despite these adverse changes, the premenopausal levels of risk factors were strong predictors of extent of calcification. With the exception of change in glucose, no risk factor changes were related to calcification. With the exception of postmenopausal SBP in relation to AC, risk factors five years after the menopause were unrelated to calcification after the premenopausal levels were entered into the models. Use of HT, statins, and diabetes and anti-hypertensive medications did not alter the associations of premenopausal risk factors and subsequent CaC and AC. The apparent weaker associations of postmenopausal risk factors are likely a function of the long incubation period of atherosclerosis. Associations of calcification and risk factors measured in close proximity to EBT may reflect the association of concurrent risk factors with previous levels. The present report to our knowledge is the only longitudinal analysis of the relationship between premenopausal risk factors and subsequent coronary and aortic calcification based on EBT in postmenopausal women.

It is likely, but unproven, that if we could prevent the development of new CaC during the transition from pre- to post-menopause, incidence of coronary disease would be substantially reduced, even into old age (Newman et al, 2002). There is little evidence, however, that lipid-lowering therapies slow the progression of CaC, at least in the short term (Walsh 2004). Evidence suggests that aggressive lipid-lowering therapy by pharmacologic or nonpharmacologic means may be required to slow the progression of subclinical disease and reduce the risk of heart disease (Berry et al, 2007; Nissen et al, 2006).

Our study has several limitations. First, because women were healthy at study entry and largely Caucasians, our findings cannot be generalized to minority groups or women who already have significant risk factors requiring pharmacologic or life style intervention. Second, women who remained in the Healthy Women Study and participated in the EBT protocol were more often married, Caucasian, and had lower BP and insulin levels than the others. However, they were similar in many other parameters and only 19 refused the initial EBT protocol. Third, we did not have EBT protocol as part of the baseline evaluation in 1983 so we did not know the women's premenopausal CaC and AC scores.

Conclusions

Our findings indicate that women can be identified in the premenopausal years as likely to have calcification in their sixties, even though their risk factor levels are below conventional levels of risk as recommended by National Cholesterol Education Program (NCEP), Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), and other groups. Prevention strategies should not await the substantial risk factor changes that occur during and after the menopausal transition (Matthews et al, 1989; Lindquist 1982).

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Mean (standard deviation) and median change in risk factors between baseline and fifth year postmenopausal evaluations and correlations between risk factors measured at baseline and fifth year postmenopausal evaluations in Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983- 2006.

Table 1

Risk Factors	Mean Risk Factors at Baseline Evaluation	Mean Risk Factors at Fifth Year Postmenopausal Evaluation	Mean and Median Change in Risk Factors Between Baseline and Fifth Year Postmenopausal Evaluations	Correlations between Risk Factors at Baseline and Fifth Year Postmenopausal Evaluations	Correlations between Risk Factors at Baseline and Change in Risk factors between Baseline and Fifth Year Postmenopausal Evaluations
BMI (kg/m ²)	24.58 (4.19)	26.59 (5.27)	2.01 (2.44), 1.60	0.89 [‡]	0.21 [‡]
LDL-C (mg/dL)	108.26 (29.20)	127.47 (34.04)	19.22 (28.64), 19.80	0.60 [‡]	-0.31 [‡]
HDL-C (mg/dL)	60.21 (14.17)	62.10 (16.31)	1.89 (10.73), 1.50	0.77 [‡]	-0.16 [‡]
Triglycerides (mg/dL)	81.86 (46.78)	112.26 (63.69)	30.40 (50.91), 22.00	0.61 [‡]	-0.11
Systolic blood pressure (mmHg)	107.62 (11.25)	117.12 (17.81)	9.50 (15.61), 8.00	0.50 [‡]	-0.15 [‡]
Diastolic blood pressure (mmHg)	71.81 (7.92)	70.54 (9.79)	-1.27 (9.16), -2.0	0.48 [‡]	-0.35 [‡]
Fasting glucose (mg/dL)	87.84 (20.23)	88.41 (16.99)	0.57 (14.08), 0.0	0.62 [‡]	-0.51 [‡]
Fasting insulin (μIU/mL)	8.36 (5.66)	14.49 (8.32)	6.13 (6.83), 4.70	0.50 [‡]	-0.13

BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol Note: All correlations are based on 297-309 women, except for insulin, which is based on 192 women.

* $p < .05$

[‡] $p < .01$

[#] $p < .001$

Table II

Cardiovascular risk factors at baseline (premenopausal) evaluation according to coronary calcification measured 14.6 years later (N = 363) in Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983 – 2006.

Unadjusted Mean (Standard Deviation) or Percentage (Number)	Coronary Calcification Groups			p-value for linear trend*
	0	1 to 10	11 to 100	
% Women in group	52.6 (191)	15.1 (55)	18.7 (68)	13.5 (49)
Age	47.6 (1.6)	47.6 (1.8)	47.4 (1.6)	NA
BMI (kg/m ²)	23.6 (3.3)	27.0 (5.4)	24.9 (4.6)	25.6 (5.2)
Lipids/lipoproteins				
LDL-C (mg/dL)	102.0 (24.3)	112.9 (31.3)	111.4 (32.7)	125.6 (34.1)
ApoB	88.8 (23.5)	97.9 (27.9)	92.0 (21.7)	107.6 (28.9)
HDL-C (mg/dL)	62.0 (13.2)	59.6 (12.4)	58.4 (13.6)	54.4 (17.0)
Triglycerides (mg/dL)	74.0 (37.2)	82.7 (44.6)	81.0 (40.1)	107.0 (68.7)
Systolic Blood Pressure (mmHg)	105.9 (10.0)	109.7 (11.6)	111.1 (14.2)	110.4 (12.6)
Diastolic Blood Pressure (mmHg)	71.2 (7.8)	72.7 (7.5)	72.7 (9.1)	72.6 (6.8)
Glucose Metabolism				
Glucose (mg/dL)	86.3 (10.0)	92.6 (41.0)	86.1 (11.1)	88.2 (11.8)
Insulin (μIU/mL)	7.3 (3.5)	8.7 (4.2)	7.5 (4.3)	10.5 (9.1)
% current smokers	18.9 (36)	25.5 (14)	35.8 (24)	49.0 (24)

* Adjusted for age

BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; ApoB = Apolipoprotein B; HDL-C = High Density Lipoprotein Cholesterol

Table III

Number of women (% row) in tertiles of baseline HDL and LDL-C according to coronary calcification groups average 14.6 years later in non-smokers from Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983-2006*

	Calcification Groups			
	0	1-10	11-100	> 100
Lowest HDL-C				
Lowest LDL-C	10 (50.0)	1 (5.0)	6 (30.0)	3 (15.0)
Middle LDL-C	14 (66.7)	4 (19.1)	2 (9.5)	1 (4.8)
Highest LDL-C	10 (32.3)	9 (29.0)	3 (9.7)	9 (29.0)
Middle HDL-C				
Lowest LDL-C	18 (64.3)	3 (10.7)	6 (21.4)	1 (3.6)
Middle LDL-C	21 (65.6)	5 (15.6)	5 (15.6)	1 (3.1)
Highest LDL-C	15 (50.0)	6 (20.0)	7 (23.3)	2 (6.7)
Highest HDL-C				
Lowest LDL-C	33 (70.2)	7 (14.9)	5 (10.6)	2 (4.3)
Middle LDL-C	19 (65.5)	2 (6.9)	5 (17.2)	3 (10.3)
Highest LDL-C	13 (52.0)	4 (16.0)	5 (20.0)	3 (12.0)

* Lowest HDL-C $\leq$ 52 mg/dl, middle HDL-C, 52 > and $\leq$ 64 mg/dl, highest HDL-C > 64 mg/dl.

Lowest LDL-C $\leq$ 94 mg/dl, middle LDL-C, 94 > and $\leq$ 117 mg/dl, highest LDL-C > 117 mg/dl.

Table IV

Cardiovascular risk factors at baseline (premenopausal) evaluation according to aortic calcification measured 14.6 years later (N = 350) from Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983-2006.

Unadjusted Mean (Standard Deviation) or Percentage (Number)	Aortic Calcification Groups			p-value for linear trend*
	0	1 to 100	100.1 to 500	
% Women in group	24.6 (86)	27.8 (97)	24.6 (86)	23.1 (81)
Age	47.3 (1.7)	47.6 (1.6)	47.6 (1.5)	47.8 (1.5)
BMI (kg/m ²)	23.9 (3.5)	24.4 (3.9)	25.4 (5.4)	24.9 (4.4)
Lipids/lipoproteins				
LDL-C (mg/dL)	96.8 (25.4)	105.7 (24.2)	111.2 (32.9)	121.3 (31.1)
ApoB	86.8 (21.6)	93.2 (25.8)	94.2 (27.3)	100.5 (25.8)
HDL-C (mg/dL)	62.6 (11.2)	62.2 (13.8)	58.1 (14.2)	55.9 (14.8)
Triglycerides (mg/dL)	72.2 (36.7)	75.0 (40.5)	81.4 (46.8)	99.9 (55.3)
Systolic Blood Pressure (mmHg)	103.5 (9.4)	106.7 (9.8)	110.1 (11.4)	111.7 (14.0)
Diastolic Blood Pressure (mmHg)	69.4 (8.0)	71.0 (7.0)	73.2 (7.2)	73.3 (8.2)
Glucose Metabolism				
Glucose (mg/dL)	87.1 (33.9)	87.7 (10.5)	86.4 (10.7)	89.2 (9.5)
Insulin (μIU/mL)	7.0 (3.5)	7.9 (3.7)	8.2 (6.8)	9.1 (5.5)
% current smokers	10 (11.6)	17 (17.5)	23 (26.7)	42 (51.9)

* Adjusted for age

BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; ApoB = Apolipoprotein; HDL-C = High Density Lipoprotein Cholesterol

Cardiovascular risk factors at fifth year postmenopausal evaluation according to coronary calcification measured 14.6 years after baseline or 5.0 years after fifth year postmenopausal evaluation (N =308) from Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983-2006

Table V

Unadjusted Mean (Standard Deviation) or Percentage (Number)	Coronary Calcification Groups			p-value for linear trend [*]
	0	1 to 10	11 to 100	
% Women in group	55.8 (172)	14.9 (46)	14.5 (50)	13.0 (40)
Age	57.2 (2.3)	57.2 (2.8)	57.0 (2.6)	56.9 (2.4)
Body Composition				
BMI (kg/m ²)	25.4 (4.1)	30.2 (6.9)	27.0 (5.1)	27.1 (5.9)
Waist circumference (cm)	78.4 (9.8)	90.6 (15.6)	82.6 (12.4)	84.2 (16.4)
Lipids/lipoproteins				
LDL-C (mg/dL)	123.3 (28.8)	132.1 (35.2)	131.4 (33.3)	134.3 (50.1)
HDL-C (mg/dL)	65.0 (16.1)	57.4 (13.9)	60.9 (15.8)	57.2 (18.2)
Triglycerides (mg/dL)	101.3 (54.3)	124.0 (67.1)	126.1 (71.0)	128.9 (79.4)
Systolic Blood Pressure (mmHg)	114.7 (16.4)	119.6 (19.7)	122.0 (20.0)	119.2 (17.0)
Diastolic Blood Pressure (mmHg)	69.7 (10.4)	70.5 (10.2)	73.1 (8.5)	71.3 (7.9)
Glucose Metabolism				
Glucose (mg/dL)	85.6 (8.8)	94.1 (28.1)	89.5 (20.1)	92.1 (20.5)
Insulin (μIU/mL)	13.3 (6.5)	17.0 (8.9)	12.2 (6.1)	18.5 (12.7)
% current smokers	9.9 (17)	13.0 (6)	24.0 (12)	30.0 (12)

* Adjusted for age

BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol

Cardiovascular risk factors at fifth year postmenopausal evaluation according to aortic calcification measured 14.6 years after baseline or 5.0 years after fifth year postmenopausal evaluation (N= 298) from Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983-2006.

Table VI

Unadjusted Mean (Standard Deviation) or Percentage (Number)	Aortic Calcification Groups			p-value for linear trend [*]
	0	1 to 100	100.1 to 500	
% Women in group	24.3 (72)	28.5 (85)	25.8 (77)	21.5 (64)
Age	56.9 (2.3)	57.1 (2.6)	57.0 (2.4)	57.6 (2.5)
Body Composition				
BMI (kg/m ²)	25.8 (4.4)	26.5 (5.4)	27.5 (6.3)	26.6 (4.8)
Waist circumference (cm)	79.7 (11.3)	80.6 (12.5)	84.2 (15.5)	82.6 (11.5)
Lipids/lipoproteins				
LDL-C (mg/dL)	115.6 (27.5)	127.2 (30.4)	126.6 (33.8)	140.5 (40.7)
HDL-C (mg/dL)	66.1 (14.7)	65.5 (16.3)	59.0 (16.9)	57.4 (15.5)
Triglycerides (mg/dL)	105.5 (50.3)	109.7 (66.0)	113.7 (65.1)	124.3 (74.6)
Systolic Blood Pressure (mmHg)	113.4 (14.6)	116.6 (17.1)	117.2 (17.4)	123.2 (20.9)
Diastolic Blood Pressure (mmHg)	70.3 (9.2)	70.2 (8.2)	69.6 (9.4)	72.2 (12.5)
Glucose Metabolism				
Glucose (mg/dL)	87.3 (22.2)	88.6 (16.6)	88.6 (11.6)	89.3 (17.0)
Insulin (μIU/mL)	13.7 (7.5)	13.5 (6.7)	16.3 (10.7)	14.4 (8.0)
% current smokers	2.8 (2)	8.2 (7)	22.1 (17)	25.0 (16)

* Adjusted for age

BMI = Body Mass Index; LDL-C = Low Density Lipoprotein Cholesterol; HDL-C = High Density Lipoprotein Cholesterol

Multivariate logistic regression models for the associations of baseline (premenopausal) risk factors independently associated with calcification 14.6 years later and medication use at the fifth year postmenopausal evaluation (step 1), and any significant fifth year postmenopausal risk factors (step 2) from Healthy Women Study, Allegheny County, Pennsylvania, USA, 1983-2006.

Table VII

Risk Factor	Calcification	
	Coronary ≥ 100 (N=49) OR (95% CI)	Aorta ≥ 500 (N=81) OR (95% CI)
Age (years)	.94 (.73 – 1.21)	1.10 (.88 – 1.36)
Premenopausal LDL-C (10 mg/dl)	1.15 (1.03 – 1.29)	1.23 (1.10 – 1.38)
Premenopausal SBP (5 mm/Hg)	1.08 (.91-1.28)	1.07 (.90 – 1.27)
Premenopausal Current smoker	2.72 (1.29 – 5.71)	4.62 (2.36 - 9.03)
Hormone use	1.33 (.63-2.80)	1.63 (.84 – 3.14)
Use of lipid, blood pressure, and diabetes agents	1.64 (.55 – 4.90)	.80 (.27-2.34)
Postmenopausal Risk Factors	None	
SBP (5 mm/Hg)		1.15 (1.04 – 1.27)

OR = odds ratio, CI = confidence interval, LDL-C = low density lipoprotein cholesterol, SBP = systolic blood pressure
Note: Candidates for step-wise entry into the model were fifth year postmenopausal BMI, LDL-C, HDL-C, triglycerides, SBP, DBP, glucose, smoking status, and age.