



Subclinical atherosclerosis in multiple vascular beds: an index of atherosclerotic burden evaluated in postmenopausal women

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Abstract

The Healthy Women Study has evaluated risk factor changes as women go through the menopause. In 274 women, measures of atherosclerosis in the coronary, aorta and carotid arteries were obtained at 8 years postmenopause using electron beam tomography and carotid ultrasound. The purpose of this study was to evaluate the association between baseline premenopausal risk factors and subclinical disease in various vascular beds and with an aggregate atherosclerosis index based on all subclinical measures. The prevalence of measurable disease for the coronaries, carotids and aorta was 45, 55 and 72%, respectively. Disease measures across these three locations were significantly correlated ($P < 0.001$). Premenopausal LDL, triglycerides, blood pressure (BP) and smoking were associated with each measure of subclinical atherosclerosis, and were strikingly associated with the number of elevated disease measures. Among 126 women taking hormone replacement therapy (HRT), there was a strong positive association between systolic BP and subclinical atherosclerosis ($P < 0.001$). No such relationship was seen among women not on HRT and this interaction was significant ($P = 0.048$). An index of subclinical atherosclerosis rather than measurement at a single arterial site may be the best estimate of disease risk. Such a measure should be evaluated for its prognostic value along with individual measures of subclinical disease. Women with lower premenopausal risk factors did not develop high levels of subclinical atherosclerosis, suggesting that atherosclerosis is a preventable disease in women. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Although symptoms of coronary artery disease (CAD) in women occur 10–15 years later than in men [1], CAD is still a leading cause of death in women over age 60 [2]. We have previously shown that women with elevated premenopausal risk factors have a greater extent of carotid intima-media thickness at postmenopause [3,4]. This suggests that women at risk to develop atherosclerosis can be identified during their premenopausal years, opening the opportunity for de-

lay or prevention of cardiovascular disease through early modification of risk factors.

The carotid arteries are easily and accurately evaluated using ultrasound. Carotid ultrasound is used repeatedly as a non-invasive measure of atherosclerosis in general [5], and as a surrogate for coronary atherosclerosis in a number of clinical trials of cholesterol lowering [6–8]. The moderate correlation between carotid and coronary atherosclerosis [9] is of a similar magnitude to the correlation between two different coronary arteries [10].

Electron beam tomography (EBT) now allows the non-invasive evaluation of the coronary arteries directly by providing a quantitative measure of coronary calcification. Coronary calcification relates to the degree of

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atherosclerosis found on pathological exam [11], and also predicts incident cardiovascular events [12–14]. In addition, EBT allows evaluation of the aorta for quantification of vascular calcification.

The Healthy Women Study (HWS) is a longitudinal study of risk factors for coronary heart disease in women as they progress through the peri and postmenopausal years. Women were recruited starting in 1983 and now are an average of 8 years postmenopause. These women underwent carotid ultrasound and EBT to evaluate the extent of atherosclerosis in the coronary, aorta and carotid arteries. This report evaluates the degree to which measures of subclinical atherosclerosis in these vascular beds correlate with each other and reports the risk factors associated with atherosclerosis in each of these vascular beds. A subclinical disease scale, which aggregates information from each of these measures is described and associated with risk factors.

2. Materials and methods

2.1. Healthy Women Study

Detailed descriptions of the HWS have been previously published [15,16]. Beginning in 1983, 541 premenopausal women aged 42–50 years, living in Pittsburgh, PA were recruited. Eligible women had diastolic blood pressures (BPs) less than 100 mmHg, were free from chronic disease requiring medication (including BP medication), were not taking hormone replacement therapy (HRT) and were menstruating within 3 months of the baseline examination. These women were followed until they ceased cycling and/or used HRT in combination for 12 months, at which time they were considered postmenopausal and re-evaluated. Evaluations were also performed at 2, 5 and 8 years postmenopause. No women had a history of a cardiovascular event, although eight women had suspected angina. All analyses were run with and without these women with no substantive differences. Thus, these women were included in the presentation here.

2.2. Clinic visits

The baseline clinic visit included height, weight, BP, and a fasting blood sample for determination of insulin, glucose and lipoproteins. Assays were performed at a central laboratory, which adheres to the quality control standards recommended by the Centers for Disease Control and National Heart Lung and Blood Institute. Standard assays were used to measure total serum cholesterol [17], total HDL cholesterol [18] and triglycerides [19]. LDL cholesterol was estimated using the Friedwald equation [20]. Serum glucose was determined

by enzymatic assay [21]. BPs were measured twice using a random-zero sphygmomanometer, and the results were averaged. Similar data were collected at visits 1, 5 and 8 years postmenopause. All women signed an informed consent that was approved by the University of Pittsburgh Institutional Review Board.

2.3. Measures of subclinical atherosclerosis

2.3.1. Carotid ultrasound

Carotid ultrasound was performed at either 5 years (49%) or 8 years (51%) post-menopause. Women were scanned consecutively as they returned for their clinic visits. A Toshiba SSA-270A scanner equipped with a 5 MH linear array imaging probe was used. Certified sonographers scanned the right and left common carotid artery, carotid bulb, and the first 1.5-cm of the internal and external carotid arteries. For each location, sonographers focused on the interfaces required to measure intima-media thickness (IMT) and any areas of focal plaque. The best images were digitized for later 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 internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of IMT. Each location was also scored for plaque. Plaque was defined as a distinct area protruding into the vessel lumen with at least 50% greater thickness than surrounding areas. The plaque index, a measure of extent of focal plaque, was created based on the size and number of plaques at each location. The plaque index has been used as a measure of focal plaque for a number of years and has been found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations [22]. Reproducibility was evaluated in 15 subjects who had their scans performed by two different sonographers. The intraclass correlation was 0.88 for IMT and 0.93 for the plaque index.

2.3.2. Electron beam tomography

Women were invited to have an EBT of the heart and the aorta after their 8-year postmenopausal exam and only seven have refused. The baseline characteristics of the women in the EBT study were similar to all women who have been in the clinic for their 8-year postmenopausal examinations. The carotid ultrasound and the EBT studies were not always done at the same visit, and the average difference in time between the two tests was 12 months. The EBT studies were done using an Imatron C150 scanner (Imatron, South San Francisco, CA). To evaluate the coronary arteries, 30–40 contiguous 3-mm thick transverse images were obtained from the level of the aortic root to the apex of

the heart. Images were obtained during maximal breath holding using ECG triggering so that each 100 ms exposure was obtained during the same phase of the cardiac cycle (80% of the RR interval). During a second pass, 6 mm contiguous images of the aorta were obtained from the aortic arch to the iliac bifurcation using a 300 ms exposure time. Calcium scores for both the heart and the aorta were calculated by the method of Agatston [23] with a densitometric program available on the Imatron C150 scanner.

Reproducibility of the coronary and aortic calcium scores was evaluated in 42 consecutive subjects selected to have a wide range of calcification values. The intraclass correlation of the coronary score was 0.99 and for the aortic score was 0.98. To assess long-term (1 year) reproducibility, 52 HWS subjects underwent replicate scans separated by 1 year. The correlation between baseline and follow-up calcification scores was 0.93 for the coronary arteries and 0.97 for the aorta.

2.3.3. Statistical methods

Testing resulted in four measures of subclinical atherosclerosis: coronary calcification, aortic calcification, carotid wall thickness and extent of carotid plaque. None of these four continuous variables were normally distributed. Because the plaque index and calcium scores are created by combining discrete areas of disease, we chose not to normalize the distributions. Univariate associations between the continuous measures were performed using Spearman correlations. In addition, each measure was divided at the 80th percentile into high and low groups. The association between this dichotomous measure and other variables was assessed using *t*-tests and Wilcoxon tests as appropriate for continuous variables, and χ^2 test for categorical variables. A number of considerations went into the choice of using the 80th percentile as the cut point. First, one of the advantages of using subclinical measures of atherosclerosis is that early disease can be detected. Accordingly, in this population of middle-aged women, a wide range of subclinical disease can be measured while the prevalence of clinically important disease is quite rare. Thus, using clinically defined cut points is of limited value here. In addition, for many of these measures such as carotid IMT, an exact cut point corresponding to clinical significance has not yet been agreed upon by the medical community. From a statistical perspective, a consistent cut point based on the distributional percentile ensures that the analyses for each vascular bed are comparable.

Information from all four subclinical measures was combined into a summary score that consisted of the number of measures (0–4) that were at or above the 80th percentile. To test a linear association between this summary score and risk factors, a linear regression model was employed for most continuous risk factors,

with the exception of highly skewed factors for which the rank-based Jonckheere–Terpstra [24] test was used. The Mantel–Haentzel χ^2 statistic was used to assess a linear association between summary score and categorical variables.

Multivariate analysis to evaluate the independent factors associated with each subclinical measure was performed using ordinal logistic regression, which allows for an ordered categorical dependent variable. Each disease measure was broken into three or four categories. Coronary calcification was categorized as 0, 1–20, or greater than 20. Aortic calcification was categorized as 0, 1–54, 55–347, or 348+. The plaque index was categorized as 0, 1, 2–3, or 4+. Average carotid IMT thickness was categorized as less than 0.73, 0.73–0.77, 0.78–0.849 or 0.85+ mm. For the summary score, the top two categories were combined due to small cell sizes, resulting in categories of 0, 1, 2, or 3+ elevated disease measures. A stepwise regression was run for each subclinical disease endpoint. Age was forced into the model and the candidate variables to enter the model were the variables in Table 2 that showed a significant univariate association with the disease measure. A final model was constructed which included all variables that were found to be independently associated with any of the subclinical disease measures. Pulse pressure was used instead of systolic BP because it was most often a stronger predictor of disease. Similarly, LDL was used instead of HDL because it was most often a stronger predictor of subclinical disease. The final model was then run for each of the subclinical measures so that comparisons could be made across the measures. For all analyses, a probability value of 0.05 or less was considered significant.

3. Results

Coronary and aortic calcification data are available for a total of 274 women. At the time of EBT testing, their average age was 59 years, they were an average of 8 years postmenopause, and 50% were taking HRT. At baseline, prior to menopause, the average cholesterol was 184 mg/dl, average HDL was 60 mg/dl, average LDL was 108 mg/dl, average BMI was 25 kg/m², and average systolic BP was 108 mmHg. Approximately 26% were current smokers at baseline. These characteristics are similar to women who did not have an EBT.

The prevalence of any measurable disease was 45% for the coronary arteries (coronary calcium > 0), 55% for the carotid arteries (plaque index > 0) and 72% for the aorta (aortic calcium > 0). The coronary calcification score ranged from 0 to 1175 with a median value of 0 and the aortic calcification score ranged from 0 to 4796 with a median value of 58 (Fig. 1). Average IMT in the carotid arteries ranged from 0.60 to 1.35 mm

with a median value of 0.77 mm. The plaque index ranged from 0 to 11 with a median value of 1.

The measures of subclinical atherosclerosis were significantly correlated with one another. Higher levels of disease in one vascular bed were associated with higher levels of disease in the other vascular beds as well (Fig. 2). The strongest correlations were between the aortic and coronary calcification scores (0.438, $P < 0.001$) and the carotid plaque index and IMT (0.577, $P < 0.001$). However, all measures were highly correlated with one another (0.215–0.577, $P < 0.001$ for all).

Premenopausal risk factors are more strongly associated with subclinical disease than postmenopausal risk factors in these women [3,4]. Thus, premenopausal risk factors were evaluated in association with each disease measure. An approximate 80th percentile cut point was used to divide each measure into 'high' vs 'low' levels. High levels of disease were defined as follows: coronary calcification, 40 or greater (80th percentile); aortic calcification, 470 or greater (80th percentile); carotid plaque index, values of 2 or greater, (69–84th percentile) and carotid IMT, 0.87 mm or greater (80th percentile). Premenopausal cardiovascular risk factors including lipids, BP and smoking were associated with each measure of subclinical atherosclerosis and in most cases, these associations were statistically significant (Table 1).

The number of disease measures above the 80th percentile was next used as a subclinical disease scale

ranging from 0 to 4. Complete data were available for 257 women. No positive disease measures were present for 129 (50%), one measure was positive for 61 (24%), two measures were positive for 39 (15%), three measures were positive for 17 (7%) and all four measures were positive for 11 (4%). Baseline premenopausal risk factors were strongly associated with the number of positive disease measures (Table 2). Mean LDL ranged from 102 mg/dl in the no disease group to 136 mg/dl in the group with four positive measures ($P < 0.001$). The prevalence of smoking ranged from 16% in the no disease group to 59% in those with three positive disease measures ($P = 0.001$). Other factors significantly associated with the subclinical disease score were total cholesterol, HDL cholesterol, HDL-2, apoprotein B, triglycerides, body/mass index, fasting insulin and glucose, systolic BP and pulse pressure.

When stepwise regression was run for each subclinical measure individually, the final models all included at least one lipid variable (LDL or total cholesterol) and one BP variable (either pulse pressure or systolic BP). To allow a comparison across each disease measure, the same model was run on the same group of participants for each disease measure (Table 3). This model included any variable that was found to be significant in any of the stepwise models. Age was forced into the model. Pulse pressure was used instead of systolic BP because it was more strongly related to most of the disease measures. Similarly, LDL cholest-

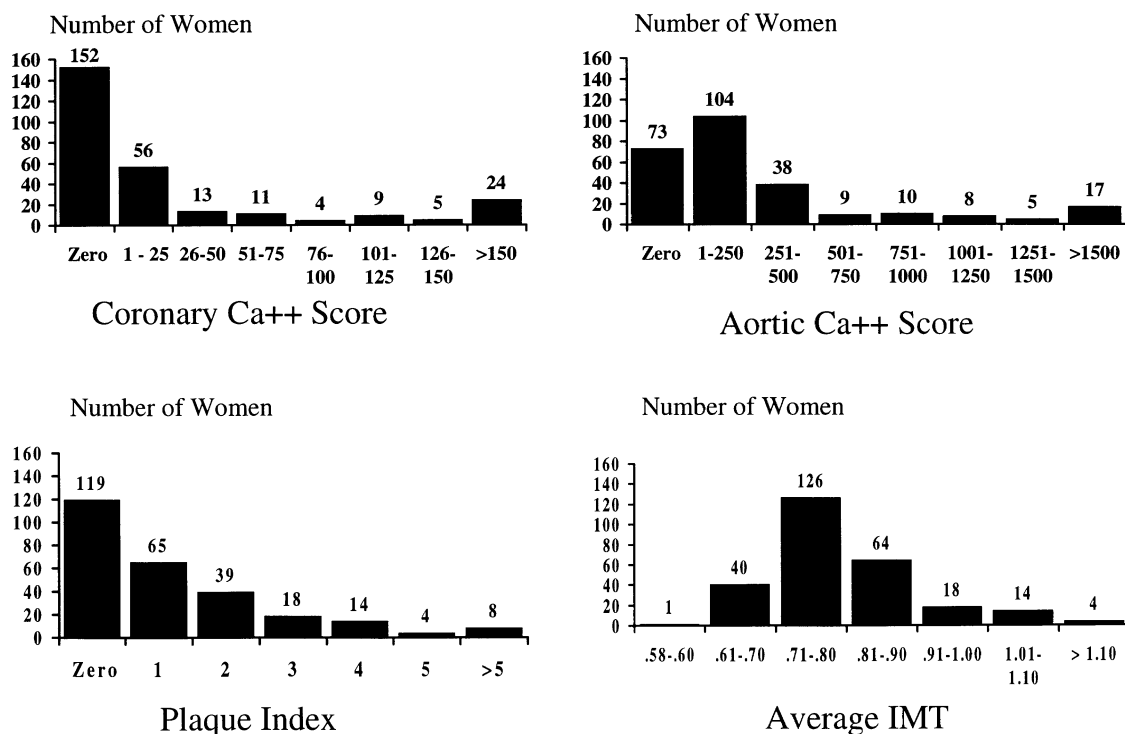


Fig. 1. Distributions of four continuous measures of subclinical atherosclerosis.

Table 1
Associations between baseline premenopausal risk factors and subclinical disease measured at 8 years postmenopause

	Coronary Ca ²⁺		P-value	Aortic Ca ²⁺		P-value	Plaque index		P-value	Average IMT		P-value
	<40 (N = 217)	≥40 (N = 57)		<470 (N = 211)	≥470 (N = 53)		<2 (N = 184)	≥2 (N = 83)		<0.87 (N = 215)	≥0.87 (N = 52)	
Mean cholesterol (mg/dl)	182	195	<0.016	181	198	<0.001	180	194	0.002	181	199	0.002
Mean HDL (mg/dl)	61	57	<0.074	61	56	<0.022	61	59	0.191	61	58	0.237
Mean HDL-2 (mg/dl)	22	19	<0.050	22	19	<0.039	22	20	0.151	22	20	0.134
Mean LDL (mg/dl)	105	118	<0.007	104	122	<0.001	104	117	0.002	105	121	0.002
Mean apoprotein B(mg/dl)	91	101	<0.004	92	98	0.085	90	98	0.026	90	105	0.001
Median triglycerides (mg/dl) ^a	65	77	<0.011	65	83	<0.001	64	77	0.013	65	85	<0.001
Mean BMI (kg/m ²) ^a	25	25	0.824	24	25	0.391	24	25	0.006	24	26	0.017
Median fasting glucose ^a (mg/dl)	86	87	0.642	86	89	0.037	86	88	0.052	86	88	0.164
Median fasting insulin	6.5	6.8	0.518	6.4	7.6	0.079	6.2	7.4	0.003	6.3	7.4	0.142
Median fibrinogen ^a	3.9	3.3	0.235	3.8	3.6	0.801	3.8	3.5	0.516	3.9	3.31	0.458
Mean systolic BP (mmHg)	107	110	0.119	107	111	0.013	107	111	0.002	107	112	0.008
Mean diastolic BP (mmHg)	72	72	0.868	71	73	0.067	72	73	0.300	72	74	0.068
Mean pulse pressure (mmHg)	36	38	0.035	36	38	0.083	35	38	<0.001	35	38	0.008
% HRT use	51.7	41.5	0.185	52.8	36.2	0.041	52.9	43.4	0.168	48.3	57.8	0.249
% Smokers	21.2	42.1	0.001	18.5	49.1	0.001	18.5	39.8	0.001	23.5	33.3	0.179
Age at baseline (years)	48	48	0.708	48	48	0.720	48	48	0.261	48	48	0.829
Age at 8 year exam (years)	59	60	0.464	59	60	0.207	59	60	0.520	59	59	0.384

HDL – High density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; BMI – body/mass index; BP – blood pressure; and HRT – hormone replacement therapy.
^a Wilcoxon test.

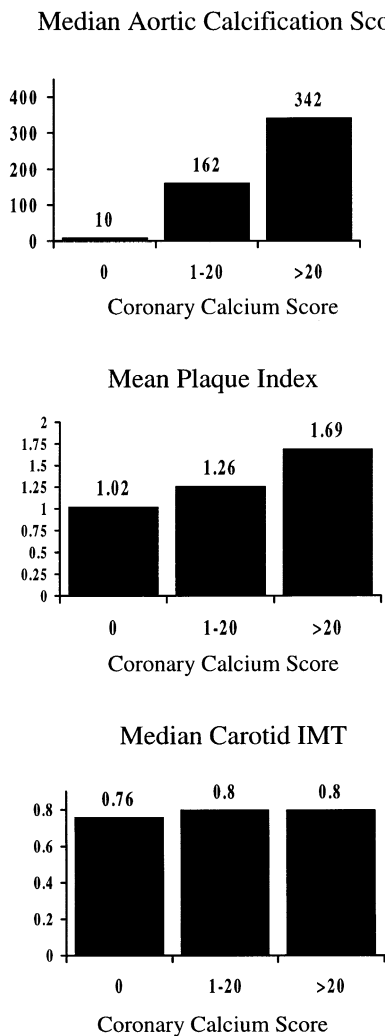


Fig. 2. Association between coronary calcium score and other subclinical atherosclerosis measures.

terol was more strongly and consistently associated to the disease measures than total cholesterol. In this final model, LDL and pulse pressure were independently associated with each disease measure (Table 3). Smoking was positively associated with each measure, although this only reached statistical significance for aortic calcification and the aggregate measure of disease. Triglycerides were positively associated with coronary calcification, average IMT and the aggregate measure of disease.

The only subclinical disease measure found to have a significant association with HRT was aortic calcification. Among women taking HRT, the median aortic calcification score was 30, compared to 109 among women not taking HRT ($P = 0.035$). This association persisted in multivariate analysis (Table 3).

The analysis was next stratified by HRT use. Of the 126 women reporting HRT use at the 8 year postmenopause exam, 78% were on a combination of estro-

gen and progesterone. Of those taking HRT, 67% had been taking HRT for at least 3 years. Among the 128 women not on HRT at year 8, 81% reported no HRT at any time during follow-up. When comparing the women who were on and off HRT at the year 8 exam, the only significant difference in premenopausal characteristics was in smoking rates. The prevalence of smoking at baseline was 33% among HRT non-users and 18% among HRT users ($P = 0.008$). In the stratified analysis, associations between baseline premenopausal risk factors and subclinical disease measures were the same for HRT non-users and users, with the exception of BP. Among women not on HRT, there were no significant associations between premenopausal BP and any measure of subclinical atherosclerosis. However, among women on HRT, there were strong positive associations between premenopausal BP and each subclinical disease measure ($P < 0.01$ for all). The most striking association was with number of positive disease measures. The average systolic BP ranged from 105 mmHg for women with no positive disease measures to 118 mmHg for women with three or more positive disease measures ($P < 0.001$). When an HRT by BP interaction term was added to the multivariate model predicting number of positive disease measures, the interaction term was significant with a P -value of 0.048.

4. Discussion

This study demonstrates that different measures of subclinical atherosclerosis are correlated with one another, even in a healthy population of middle-aged women. Traditional cardiovascular risk factors were related to disease in each vascular bed, underscoring that atherosclerosis is a systemic disease affecting the vascular system as a whole. A higher prevalence of measurable disease was found in the aorta and carotid arteries than in the coronary arteries, suggesting that disease can be detected earlier in these areas. This observation in vivo is consistent with pathology studies, which have shown that disease develops earlier in these areas [25,26]. The high prevalence of aortic atherosclerosis in middle-aged women has also been noted in epidemiological studies using chest X-rays to identify aortic calcification [27]. The high correlation between coronary disease and both aortic and carotid disease suggests that early aortic and carotid disease may predict subsequent coronary atherosclerosis. Thus, it is possible that some of the women with aortic calcification, but little coronary calcification will, over time, develop atherosclerosis in the coronary arteries.

The combination of disease in different vascular beds was associated with significantly higher levels of key risk factors, especially LDL cholesterol, apoprotein B, triglycerides, systolic BP and cigarette smoking. How-

ever, the mean level of risk factors were within normal limits for the vast majority of these women. The 129 women (Table 2) with scores less than the 80th percentile for all disease measures had low risk factor levels at premenopause, ≈ 8 –12 years prior to their disease measurements. This includes a low LDLc (102 mg/dl), high HDLc (63 mg/dl), low triglycerides (89 mg/dl, 0.994 mmol/l), and low systolic BP (106 mmHg). These findings are consistent with recommended guidelines for heart disease prevention and suggest that atherosclerosis may be preventable if risk factors can be maintained at lower levels.

The value of measures of subclinical atherosclerosis is their ability to identify subjects at risk early in the course of atherosclerosis so that risk factor modification can be instituted in time to delay or prevent cardiovascular events. Measures of peripheral disease such as the ankle arm index [28–30], and carotid IMT [31,32], consistently predict mortality and incident cardiovascular events. Coronary calcification also has been shown to predict cardiovascular events [12–14]. Important future work will be to compare the association between these various measures of subclinical atherosclerosis and outcome, both individually and in combination. It is possible that a combination of subclinical measures may yield the best information, and the analysis presented here demonstrates one way in which various subclinical disease measures can be combined. Presence of disease in multiple vascular beds is likely a measure of both the severity and the extent of disease. In the Cardiovascular Health Study, prevalence

of any subclinical disease (a combination of measures across vascular beds) was independently associated with increased risk of clinical cardiovascular disease [33]. We have clearly shown here that the greater number of vascular beds involved, the higher the risk factor levels. Although the numbers were small, there was almost a 50 mg difference in LDLc between women who had no disease by any measure and those who had disease by four measures.

The risk factors for disease in each of the vascular beds were similar in this study. An association between HRT use (usually a combination of estrogen and progesterone) and disease was noted for calcification of the aorta only. The association between HRT use and both clinical and subclinical disease remains controversial [34]. In the Atherosclerosis Risk in Communities study, HRT use was associated with thinner carotid IMT, but not thinner IMT in the popliteal arteries [35]. There could be a difference in the effects of hormones on subclinical disease for estrogen alone as compared to combined estrogen–progesterone therapy, but this study had too few women on estrogen alone to evaluate this.

An interesting finding reported here is the interaction between HRT use and systolic BP. Higher levels of systolic BP (even though well within the normal range), were more consistently associated with subclinical disease in women on HRT compared to those not on HRT. Progestins oppose the actions of estrogens through down-regulation of estrogen receptors [36] and there is evidence that progestins induce vasoconstriction

Table 2
Association between baseline premenopausal risk factors and extent of subclinical atherosclerosis at 8-years postmenopause

	Number of diseases measures > 80th percentile					P-value
	0 (N = 129)	1 (N = 61)	2 (N = 39)	3 (N = 17)	4 (N = 11)	
Mean cholesterol	178	182	190	203	218	<0.001
Mean HDL (mg/dl)	62	62	56	52	62	0.009
Mean HDL-2 (mg/dl)	23	23	18	17	22	0.018
Mean LDL (mg/dl)	102	104	116	127	136	<0.001
Mean apoprotein B (mg/dl)	89	89	95	111	104	0.005
Median triglycerides ^a	63	67	75	101	88	<0.001
Mean BMI (kg/m ²)	24	25	26	26	23	0.008
Median glucose(mg/dl) ^a	85	87	86	93	86	0.046
Median fasting insulin ^a	6.2	6.7	7.3	9.6	7.5	0.032
Median fibrinogen ^a	3.9	3.9	3.5	2.4	3.4	0.357
Mean systolic BP (mmHg)	106	108	111	114	107	0.002
Mean diastolic BP (mmHg)	71	72	73	74	72	0.619
Mean pulse pressure (mmHg)	34	37	39	40	35	<0.001
% HRT use	54	47	42	47	50	0.734
% Smokers	16	16	41	59	55	<0.001
Age at baseline (years)	48	48	48	48	48	0.655
Age at 8-year exam (years)	62	62	62	61	62	0.564

HDL – High density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; BMI – body/mass index; BP – blood pressure; and HRT – hormone replacement therapy.

^a Jonckheere–Terpstra Test.

Table 3
Association of risk factors with subclinical disease measures – comparison of multivariate ordinal logistic regression models

	Coronary calcification quartile (N = 237)		Aortic calcification quartile (N = 237)		Plaque index quartile (N = 237)		Average IMT quartile (N = 237)		Number of positive disease measures (N = 237)	
	OR	95%C.I.	OR	95%C.I.	OR	95%C.I.	OR	95%C.I.	OR	95%C.I.
Pulse pressure (10 mmHg increase)	1.4	1.0, 2.0	1.5	1.1, 2.1	1.7	1.2, 2.4	1.7	1.2, 2.4	1.9	1.3, 2.7
Smoking	1.8	0.99, 3.2	2.3	1.3, 4.2	1.7	0.96, 3.0	1.3	0.72, 2.3	2.9	1.6, 5.2
LDL cholesterol (25 mg/dl increase)	1.3	1.1, 1.7	1.5	1.2, 1.9	1.4	1.1, 1.7	1.3	1.0, 1.6	1.4	1.1, 1.8
Triglycerides (25 mg/dl increase)	1.2	1.0, 1.4	1.0	0.91, 1.2	1.1	0.97, 1.3	1.2	1.0, 1.4	1.2	1.1, 1.4
HRT use	0.73	0.43, 1.2	0.60	0.37, 0.97	0.75	0.46, 1.2	0.98	0.60, 1.6	0.73	0.44, 1.2
Age (5 year increase)	0.79	0.34, 1.8	1.2	0.57, 2.6	1.1	0.50, 2.4	1.1	0.50, 2.3	1.3	0.59, 3.0

Additional variables considered were: cholesterol, HDL, HDL-2, apoprotein B, BMI, fasting glucose and systolic BP. HDL – High density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; and BP – blood pressure. The odd ratios below the dotted line represent the results achieved when the indicated lipid value is placed in the regression model in place of LDL.

of estrogenized vessels [37]. The observed interaction between HRT use and BP in association with subclinical disease seen in this study may provide clues to possible hemodynamic effects of an estrogen/progestin combination. However, the numbers evaluated here are small, and the results should be treated with caution.

Atherosclerosis is a diffuse disease, which does not affect each vessel in an identical fashion. Thus, one coronary artery can be totally occluded while an adjacent artery can be relatively normal. Because of this, the correlations between various disease measures are significant, but not overwhelmingly high. This is the reason that combining information from a number of vascular beds may provide better information than focusing on one measure alone. This analysis has demonstrated that a combination of subclinical measures provided a more consistent association with risk factors than any individual measure of subclinical disease. In the analysis presented here, an evaluation of the legs could have been added by doing ankle BPs, which provide an accurate evaluation of occlusive disease to the lower extremities [38]. However, the prevalence of an ankle/arm index < 0.9 is very low in middle aged and younger people [39]. Ankle BPs were thus not done in this population of middle-aged women. In older populations, the ankle BP could be used to provide information on yet another vascular bed. This analysis represents one of many ways to combine information from various subclinical tests. An optimum index of atherosclerotic burden might eventually use different cut points for the various measures or might weight the individual measures differently. Refinement of this index will require collecting these data simultaneously in a number of different populations as is currently being done in the NHLBI Multi-Ethnic Study of Atherosclerosis.

In conclusion, these data demonstrate that atherosclerosis is a systemic disease with non-invasive measures correlating across vascular beds. An index of subclinical atherosclerosis rather than measurement at a single arterial site may provide a better estimate of disease risk. Such a measure should be evaluated for its prognostic value along with individual measures of subclinical disease. Second, traditional risk factors are powerful determinants of subclinical atherosclerosis. Women with lower premenopausal risk factors (in line with current public health recommendations) did not develop high levels of subclinical atherosclerosis. This is strong evidence that atherosclerosis is a preventable disease in women.

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