

# Coronary and Aortic Calcification Among Women 8 Years After Menopause and Their Premenopausal Risk Factors

## The Healthy Women Study

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**Abstract**—In the Healthy Women Study, the relationship between cardiovascular risk factors measured premenopausally at age 48, use of hormone therapy, and coronary and aortic calcification at age 58 were evaluated among 169 women. Approximately 63% of women had no coronary calcification, but only 29% had no aortic calcification. Coronary calcification and aortic calcification were positively correlated with each other. There was a very strong association between low density lipoprotein cholesterol (LDL-C) level and coronary calcification. Among women with premenopausal levels of LDL-C <100 mg/dL, only 9% had a coronary calcium score  $\geq$ 101 compared with 30% of women with an LDL-C >160 mg/dL. Only 5% of women with a high density lipoprotein cholesterol (HDL-C) level >60 mg/dL had high coronary scores. The level of HDL<sub>2</sub>-C was especially strongly inversely related to coronary calcium scores. Cigarette smoking was a very important determinant of both high aortic and high coronary calcium scores. Other risk factors associated with greater coronary calcium were higher systolic blood pressure, triglycerides levels, and blood glucose. Use of hormone replacement therapy was associated with less coronary calcium (NS). For both hormone replacement therapy users and nonusers, the levels of LDL-C and HDL-C measured premenopausally were predictors of coronary and aortic calcium scores. Thus, risk factors evaluated premenopausally are powerful predictors of coronary and aortic calcification, a marker of atherosclerosis, measured 8 years after menopause, 11 years later in these women. (*Arterioscler Thromb Vasc Biol.* 1999;19:2189-2198.)

**Key Words:** coronary artery disease ■ coronary calcification ■ lipids ■ smoking ■ hormone replacement therapy

The development of new techniques to measure the extent of subclinical cardiovascular disease, such as carotid duplex scanning and electron beam CT (EBCT), has provided important new approaches to study the relationship of risk factors and cardiovascular disease. In this article, we report the relationship between cardiovascular risk factors measured premenopausally and coronary and aortic calcification for 168 women, as measured by EBCT, in the Healthy Women Study (HWS) at the eighth postmenopausal visit.<sup>1,2</sup>

In previous reports from the HWS, we evaluated the determinants of changes in cardiovascular risk factors from the premenopause, perimenopause, and postmenopause.<sup>3</sup> There was an increase in LDL cholesterol (LDL-C), little change in total HDL-C, a substantial decline in HDL<sub>2</sub>-C, and an increase in HDL<sub>3</sub>-C. The women gained  $\approx$ 1 pound per year from the perimenopause through the postmenopausal years. Weight gain was associated with a substantial increase in LDL-C, triglycerides, and systolic blood pressure and a decrease in HDL-C levels.<sup>4</sup>

In this article, we evaluated 2 hypotheses. First, we predicted that the cardiovascular risk factors that predict

clinical cardiovascular disease in elderly women would also predict coronary and aortic calcification in middle-aged women. The extensive risk factor assessment was completed when the women were premenopausal and were free from cardiovascular and metabolic diseases, including hypertension, diabetes, and thyroid disease. Second, we predicted that use of postmenopausal hormone replacement therapy (HRT) would influence the relationships between lipids and coronary calcification, given that HRT affects lipid metabolism.

Epidemiological studies have shown that intima-media thickness in the carotid artery is greater in men than in women and that this thickness increases with age in both sexes.<sup>5-7</sup> The extent of carotid plaque also increases from premenopause to postmenopause and is correlated with traditional cardiovascular risk factors. In postmenopausal women, the extent of carotid intima-media thickness is a strong predictor of the subsequent risk of clinical coronary disease.<sup>5</sup>

The extent of aortic calcified plaque as measured by routine x-rays in either the thoracic or abdominal aorta increases with age in women from the premenopause through the postmenopause.<sup>8,9</sup> Women who had undergone a bilateral

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oophorectomy had a 5-fold greater risk of having calcifications of the abdominal aorta. Calcification in both the thoracic and abdominal aortas has been associated with an increased risk of cardiovascular disease among both men and women.<sup>10</sup>

The measurement of coronary calcification by EBCT is a more direct approach for noninvasively measuring the extent of coronary artery disease.<sup>11</sup> Previous studies have shown that coronary artery calcification is related to the extent of coronary atherosclerosis and is greater in patients with myocardial infarction.<sup>12,13</sup> Coronary artery calcification increases with age in both sexes and is substantially greater in men than in women, especially in the younger age groups.<sup>14,15</sup>

The extent of coronary calcification in the coronary arteries has been associated with a substantial increase in risk of clinical coronary heart disease.<sup>16,17</sup> The amount of calcification found on EBCT examination was much greater in women who had coronary heart disease compared with women without this disease.<sup>15</sup> Thus, in the 50- to 59-year age group, only 14% of women without clinical coronary artery disease had coronary calcium compared with 40% of the women with a history of or symptomatology related to clinical coronary artery disease.

There have been only 2 previous population-based studies that used EBCT in younger individuals. Preliminary data from the CARDIA (Coronary Artery Risk Development In young Adults) study of 128 participants aged 28 to 40 years noted that the prevalence of any calcium in the coronary arteries was 52% in black men, 30% in black women, 48% in white men, and 32% in white women.<sup>18</sup> In the Muscatine (Iowa) Study, the extent of coronary artery calcification by EBCT was evaluated in 197 men and 187 women who had risk factors measured at a mean age of 15 years and again at ages 27 and 33.<sup>19</sup> The subjects were between 29 and 37 years at the time of the EBCT measurements. The prevalence of coronary calcification was 31% in men and 10%<sup>20</sup> in women. Risk factors measured in young adult life that were related to calcification included weight, body mass index (BMI), skin-fold thickness, systolic blood pressure, diastolic blood pressure, higher triglyceride levels, and lower HDL-C.

## Methods

Detailed descriptions of the HWS have been previously published.<sup>2,21</sup> A total of 541 premenopausal women were recruited in 1983 and 1984 to study the changes in their biological and behavioral characteristics as they progressed from premenopause to perimenopause to postmenopause. The women (aged 42 to 50 years) were recruited from driver's license lists within selected zip codes in Allegheny County, Pennsylvania. They were initially interviewed by telephone to determine eligibility: experienced menstrual bleeding within the previous 3 months, had not undergone surgically induced menopause, had a diastolic blood pressure <100 mm Hg, and were not using medications known to influence the risk factors in the study, such as lipid-lowering agents, insulin, thyroid hormone, estrogens, antihypertensive drugs, or psychotropic medications. Approximately 90% of the women contacted agreed to the telephone interview, and 60% of the eligible women were recruited to the study.

Women were evaluated in the clinic after a 12-hour fast. Blood samples were obtained for measurement of serum lipoproteins and apolipoproteins. Blood pressure was measured according to the MRFIT (Multiple Risk Factor Intervention Trial) protocol. A glucose load of 75 g was administered with blood sampling before and 2 hours afterward. A 24-hour food-recall interview was administered by trained nutritionists.

Women reported their menstrual status on postcards that were completed each month. Menopause was defined as the cessation of menses for 12 months or the cessation of menses and initiation of HRT for a combined total of 12 months. Each menopausal woman was then scheduled for a follow-up evaluation, which was identical in most respects to the baseline evaluation. Menopausal evaluations were done at 1, 2, 5, and 8 years after menopause. Levels of total cholesterol, HDL-C, HDL subfractions, and triglycerides were measured in the lipid laboratory of the Graduate School of Public Health, which had been certified by the Centers for Disease Control and Prevention, Atlanta, Ga. LDL-C was estimated with the Friedewald equation. Levels of apoA1 and apoB were measured by electroimmunoassay. Plasma glucose levels were determined by enzymatic assay and plasma insulin by radioimmunoassay. Physical activity was measured in kilocalories per week on the basis of the women's report of their use of leisure-time physical activity during the previous week.<sup>2</sup> Carotid duplex scanning was also done at either the fifth or the eighth postmenopausal examination.<sup>22</sup>

Follow-up to date has been excellent. At the time of eligibility for the eighth postmenopausal examination, there have been 7 deaths and 51 women have dropped out, 32 of the 51 between baseline and the first postmenopausal examination. Of the remaining eligible women, 109 are active study subjects but have not yet become eligible for their eighth examination, and of the remaining 374, 305, or 82%, have had a clinical evaluation and 72, or 18%, are being followed up by mail or telephone contact.

Women after their eighth postmenopausal examination were invited to have an EBCT of the heart and the aorta. To date, only 7 women invited for the EBCT study have refused the examination. The characteristics of the women in the EBCT study are similar to all women who have visited the clinic for their eighth postmenopausal examination. The EBCT studies were performed with an Imatron C150 EBCT scanner (Imatron). We obtained 30 to 40 contiguous, 3-mm-thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath-holding by 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 (30-ms exposure) were obtained from the aortic arch to the iliac bifurcation. Calcium scores were calculated by the method of Agatston et al<sup>23</sup> with a densitometric program available on the Imatron C150 scanner.

In a previous report, we demonstrated very high reproducibility of both the coronary and aortic scans. The reproducibility of both coronary arteries was extremely high, with an intraclass correlation of  $\approx 0.99$  for the coronary score and of  $\approx 0.98$  for the aortic score.<sup>24</sup> These high correlations are partially due to the wide range of calcification noted in these studies.

The distribution of calcium scores in both the aorta and coronary arteries was very skewed, and there is no ideal method of normalizing these scores. For example, in this study, 63% of the women had a coronary calcium score of zero; the 75th percentile was a calcium score of 13; the 90th percentile, 138; and the 95th percentile, 332. Likewise for the aorta, 29% had scores of zero; the 50th percentile was a score of  $\approx 45$ ; the 90th percentile, 770; and the 95th percentile, 1721. In the analysis we therefore treated the calcium score as a discrete rather than a continuous variable. The coronary calcium scores were divided into zero, 1 to 10, 10 to 100, and 101 or greater. The aorta scores were divided into zero, 1 to 300, or 300+.

Statistical analysis was conducted using the SPSSX statistical packages. The frequency distribution of each of the independent variables was evaluated. Logarithmic transformation was used on skewed measures and nonparametric tests were run when the variables were not normally distributed. Independent *t* tests, 1-way ANOVA, and tests of linearity were conducted.

## Results

### Characteristics of the Study Sample

There were 168 women who had detailed EBCT evaluations. There were 166 women who had scans of the aorta. The mean age at baseline was 48 years and at the eighth postmenopausal visit, at the time of the EBCT, 59 years. There was an average

**TABLE 1. Baseline Characteristics of Women in the EBCT Study, n=169**

	n	%
Age, y*	48, 59	
White	154	91
Black	14	08
Married	125	74
Education: college graduate	84	50
HRT at eighth postmenopausal visit	84	50
Estrogen+progesterone	66	39
Cigarette smoker (baseline)	47	28
LDL-C, mg/dL	108	
HDL-C, mg/dL	60	
Total cholesterol, mg/dL	184	
Triglycerides, mg/dL	81	
Fasting glucose, mg/dL	87	
Systolic blood pressure, mm Hg	108	
Diastolic blood pressure, mm Hg	71	
BMI, kg/m <sup>2</sup>	24.5	
Caloric intake	1703	
Fat, % of total calories	39	
Saturated	13	
Polyunsaturated	06	
Cholesterol intake, mg	300	
Calcium, mg	800	
Alcohol, g	9	
kcal expended in exercise during past week	1584	

Average age at baseline was 48 years; at the eighth postmenopausal visit, 59 years.

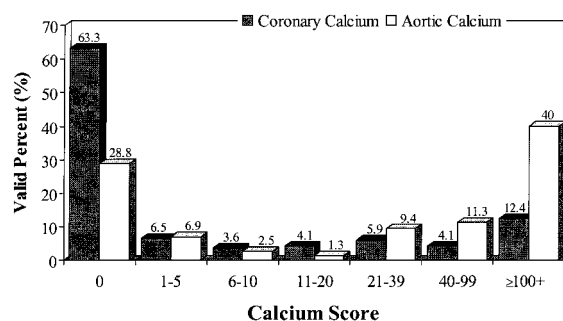
of 11 years between baseline and EBCT examinations. Ninety-one percent of the participants were white (Table 1), and 50% of the women had a college education or higher. At the eighth postmenopausal examination, ≈50% of the women were on HRT (84), and 66 of the 84 (79%) were on estrogen and progesterone (Table 1). At the baseline examination, 49 of the women (28%) were cigarette smokers. The distribution of other risk factors at baseline is also shown in Table 1.

**Prevalence of Calcification**

There was a much higher prevalence of calcification in the aorta compared with that in the coronary arteries. Sixty-three percent of the women had no calcification in the coronary arteries compared with only 27% who had no calcification in the aorta (Figure 1). There was a very high correlation between coronary and aortic calcium scores, *r*=0.44 (*P*=0.001). For example, of women who had a coronary calcium score of zero, 37% also had a zero aortic calcium score, whereas for those who had coronary calcium scores ≥101, 71% had aortic calcium scores >300 and only 5% had a zero aortic calcium score (Figure 2).

**Risk Factors for Aortic and Coronary Calcification**

The distribution of risk factors for both coronary and aortic calcium scores is shown in Tables 2 and 3. The LDL-C, HDL-C, HDL<sub>2</sub>-C, systolic blood pressure, 2-hour blood

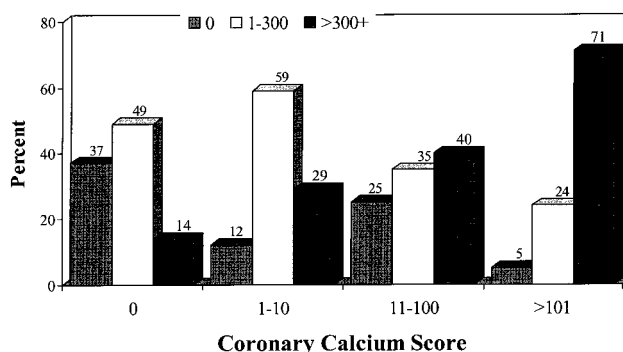


**Figure 1.** Aortic and coronary calcium scores.

glucose levels, triglycerides, apoB, and BMI were significantly related to coronary calcification scores (Table 2). These same risk factors were also related to aortic calcium scores, except for a weaker association with BMI and 2-hour glucose, and a significant association with fasting glucose (Table 3). Serum insulin was not related to either aortic or coronary calcification.

There was a very strong relationship between baseline LDL-C levels and coronary calcium scores. Seventy-one percent of the women with an LDL-C <100 mg/dL had no coronary calcification, whereas for women with an LDL-C >160 mg/dL, only 20% had a zero calcium score and 30% had scores ≥101. There were 21 women who had coronary calcium scores ≥101. Only 3 (or 14%) of these 21 women had a high LDL-C (≥160 mg/dL) at their premenopausal examination (Figure 3) because only 10 women had an LDL-C ≥160 mg/dL.

Women with a lower HDL-C had a much higher prevalence of coronary calcification. Thirty-two percent of the women with an HDL-C <45 mg/dL had no coronary calcium compared with 77% of those with an HDL-C >60 mg/dL (Figure 4). Similarly, 32% of the women with an HDL-C <45 mg/dL had a coronary calcium score ≥101 compared with ≈5.3% of those with an HDL-C >60 mg/dL. The association of aortic calcification and HDL-C was similar to that for coronary calcium scores for women with an HDL-C <60 mg/dL: 40% had aortic calcium scores >300 compared with only 11% for women who had an HDL-C >60 mg/dL (*P*=0.000). The association of HDL-C and coronary calcification was much stronger for HDL<sub>2</sub>-C compared with HDL<sub>3</sub>-C (Table 2). Both HDL<sub>2</sub>-C and HDL<sub>3</sub>-C were significantly related to aortic calcification (Table 3). We also evaluated the relationship between aortic and coronary cal-



**Figure 2.** Comparison of aortic total calcium score with coronary total calcium score.

**TABLE 2. Baseline Risk Factor Level by Coronary Calcium Scores at Eighth Postmenopausal Visit**

Coronary Calcium Score	n	LDL-C, mg/dL	HDL-C, mg/dL	HDL <sub>2</sub> -C, mg/dL	HDL <sub>3</sub> -C, mg/dL	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	BMI, kg/m <sup>2</sup>
0	106	102	63	24	40	106	70	24
1-10	17	112	59	19	40	112	74	29
11-100	24	115	57	18	39	109	73	24
101+	21	129	50	14	36	112	72	26
Total	168	108	60	21	39	108	71	25
<i>P</i> (linearity)		0.0001	0.0001	0.0000	0.0735	0.0126	0.1561	0.0320
	n	Glucose, mg/dL	2-h Glucose, mg/dL	Triglycerides, mg/dL	ApoB, mg/dL	ApoA1, mg/dL	Insulin, μU/dL	
0	106	86	88	73	87	146	7	
1-10	17	87	88	96	96	145	10	
11-100	24	86	92	84	94	141	6	
101+	21	89	102	106	106	137	9	
Total	168	87	90	81	92	144	8	
<i>P</i> (linearity)		0.4484	0.0467	0.0021	0.0029	0.0508	0.3023	

cium scores as a continuous variable and risk factors by using Spearman rank correlations (see Table 7 in the Appendix). The results are similar to the categorical analysis shown in Tables 1 and 2.

### Use of HRT and Other Drug Therapies

At the time of the first postmenopausal examination, 34% of the women were on HRT; at the second postmenopausal examination, 38%; at the fifth postmenopausal examination, 49%; and at the eighth postmenopausal examination, 50%. Of those women who were on HRT at the eighth postmenopausal examination, 52% had been on HRT at the first, 61% at the second, and 87% at the fifth postmenopausal examination. Twenty-two of 95 women (23%) on HRT at the first postmenopausal examination had stopped hormone therapy by the eighth postmenopausal examination. Most of the women (78%) were on a combination of estrogen and progesterone at the eighth postmenopausal examination. Only 7% of women were on lipid-lowering drug therapy at the eighth postmenopausal examination, 9% were on antihyper-

tensive drug therapy, and 8% were on thyroid medication. There were 3 women who reported drug therapy for diabetes (1.8%), and 4% were on major psychiatric drugs. There was no statistically significant difference in the extent of coronary ( $P=0.18$ ) or aortic ( $P=0.09$ ) calcification between hormone users and nonusers.

The relationship between HRT and LDL-C at baseline was evaluated by dividing the participants into those with an LDL-C <130 mg/dL and those with an LDL-C >130 mg/dL (Table 4) and then comparing the extent of coronary or aortic calcification by HRT use. The measurements at baseline, as noted, were premenopausal and before the women were placed on HRT, usually at least 3 to 4 years later. As noted in Table 4, for both HRT users and nonusers, the LDL-C level was an important significant determinant of the extent of coronary calcification. There was an ≈10-fold difference in the prevalence of coronary calcium scores ≥101 between those with an LDL-C <130 mg/dL on HRT compared with women with an LDL-C >130 mg/dL and not on HRT.

**TABLE 3. Baseline Risk Factor Level by Aortic Calcium Scores at Eighth Postmenopausal Visit**

Aortic Calcium Score	n	LDL-C, mg/dL	HDL-C, mg/dL	HDL <sub>2</sub> -C, mg/dL	HDL <sub>3</sub> -C, mg/dL	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	BMI, kg/m <sup>2</sup>
0	45	97	61	21	40	105	69	24
1-300	72	106	63	23	40	107	71	24
>300+	42	124	53	16	37	111	72	25
Total	159	108	60	21	39	108	71	25
<i>P</i> (linearity)		0.0000	0.0068	0.0208	0.0447	0.0051	0.0767	0.2885
	n	Glucose, mg/dL	2-h Glucose, mg/dL	Triglycerides, mg/dL	ApoB, mg/dL	ApoA1, mg/dL	Insulin, μU/dL	
0	45	83	89	77	87	146	8	
1-300	72	87	88	72	90	144	7	
>300+	42	89	97	102	99	142	8	
Total	159	86	91	82	92	144	8	
<i>P</i> (linearity)		0.0064	0.1598	0.0118	0.0349	0.2944	0.4326	

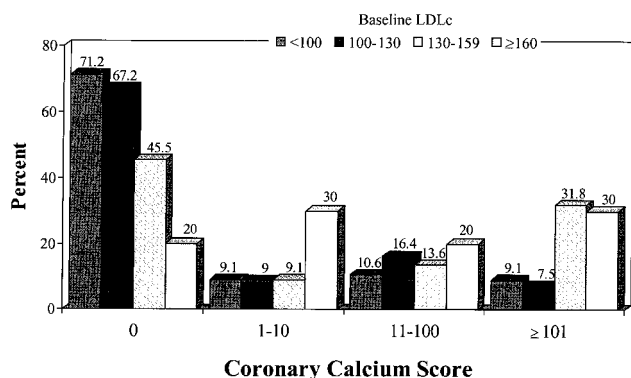


Figure 3. Baseline LDL-C by coronary calcium score.

The association of LDL-C and HRT use at the eighth postmenopausal examination and aortic calcification was very similar to that for coronary calcification (not shown). The prevalence of aortic scores >300 varied from 17% for women with an LDL-C <130 mg/dL who were on HRT at the eighth postmenopausal examination to 64% (9 of 14) for women with an LDL-C >130 mg/dL who were not on HRT. The relationship between LDL-C and the extent of aortic calcification was significant for women on and not on HRT (data not shown).

We performed a similar analysis by using HDL-C cutoff values of >60 and <60 mg/dL at baseline. Women with an HDL-C <60 mg/dL had a much higher prevalence of high coronary calcium scores and were much more likely to have some coronary calcification. Forty-six of the 86 women on HRT (53%) had an HDL-C >60 mg/dL at baseline, and their prevalence of high coronary calcium scores was only 4%. Only 6% of women with an HDL-C >60 mg/dL who were not on HRT (n=32) had a high coronary calcium score, ie, ≥101. An HDL-C >60 mg/dL was associated with a very low risk of high coronary or aortic calcium scores, irrespective of the use of HRT.

The distribution of coronary calcification by LDL-C and HDL-C was then evaluated. We divided the LDL-C into <130 or >130 mg/dL and the HDL-C into <60 or >60 mg/dL. The prevalence of both no calcification and of high scores was strongly related to the combinations of LDL-C and HDL-C. Only 21% of women in the high-risk group with an LDL-C >130 mg/dL and an HDL-C <60 mg/dL (n=24) had no coronary calcium, and 9 of these (38%) had a coronary calcium score ≥101. On the other hand, for the low-risk women with an LDL-C <130 mg/dL and an HDL-C >60 mg/dL (n=69; 41% of the women), only 3 (4%) had coronary calcifications ≥101 (an ≈9-fold difference in the prevalence of high calcium scores). Similarly, 77% of these low-risk women (ie, with an LDL-C <130 mg/dL and an HDL-C >60 mg/dL) had no coronary calcification. The results with regard to aortic calcification were similar. Fourteen of the 23 women (62%) with an LDL-C >130 mg/dL and an HDL-C <60 mg/dL had aortic calcium scores ≥300 compared with 6 of 65 (10%) with an LDL-C <130 mg/dL and an HDL-C >60 mg/dL, a 6-fold difference.

### Cigarette Smoking

Cigarette smoking at baseline (premenopausal) was very strongly associated with both coronary and aortic calcifica-

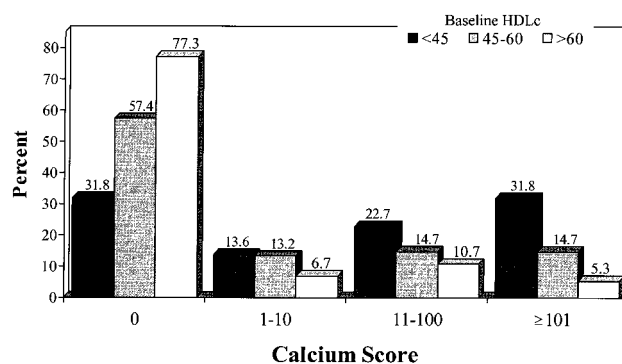


Figure 4. Baseline HDL-C by coronary calcium score at eighth postmenopausal examination.

tion. There was an ≈3-fold higher prevalence of high coronary scores ≥101 among cigarette smokers compared with non-cigarette smokers. Nonsmokers had a much higher prevalence of zero calcium scores in the coronary arteries (69%) and aorta (35%, Figure 5).

There was also a very strong interrelationship between LDL-C levels, cigarette smoking, and calcium scores. Of the cigarette smokers at baseline with an LDL-C >130 mg/dL, 136 (46%) had coronary calcium scores ≥101 compared with only 6% of 101 women who had an LDL-C <130 mg/dL and who were nonsmokers at baseline, again about a 7-fold difference. The relationship with aortic calcification was similar. Cigarette smokers with an LDL-C >130 mg/dL (8 of 11, or 73%) had aortic calcium scores ≥300 compared with only 17% (16 of 96) who were nonsmokers and had an LDL-C <130 mg/dL, an ≈5-fold difference.

We then further subdivided the population on the basis of LDL-Cs >130 or <130 mg/dL, HDL-Cs >60 or <60 mg/dL, and as cigarette smokers or non-cigarette smokers at the baseline examination. Because of the relatively small number of individuals in any 1 cell, we analyzed the data by the absence or presence of coronary calcification and also by scores ≥101. Of the smokers with an LDL-C >130 mg/dL and an HDL-C <60 mg/dL (n=10), 9 (90%) had some coronary calcification and half had coronary calcium scores ≥101. In contrast, for the 56 nonsmokers with an LDL-C <130 mg/dL and an HDL-C >60 mg/dL, only 11 (20%) had any coronary calcification and only 4% had coronary calcium scores >101. Approximately 1/3 of the women in this study would be classified as being at very low risk (ie, nonsmokers with an LDL-C <130 mg/dL and an HDL-C >60 mg/dL). They had very little coronary and aortic calcification at their eighth postmenopausal examination (Table 5).

### Fasting Triglyceride Levels

There was a significant association between fasting blood triglyceride levels and both aortic and coronary calcification (Tables 2 and 3). Women who had baseline fasting triglyceride levels <100 mg/dL were at low risk of coronary and aortic calcification: 69% had no coronary calcification and 30% no aortic calcification (not shown).

We evaluated the relationship between triglyceride levels >100 and <100 mg/dL by LDL-C for participants with an HDL-C <60 mg/dL. Women with an HDL-C >60 mg/dL had practically no significant coronary artery calcification, irrespective of their LDL-C or triglyceride levels. As shown

**TABLE 4. Relationship of Baseline LDL-C Level and HRT Use at Eighth Postmenopausal Examination to Coronary Calcification\***

	HRT Use	n	Coronary Calcium Score							
			0		1-10		11-100		>101	
			n	%	n	%	n	%	n	%
LDL-C <130 mg/dL	Yes	68	51	75	4	06	10	15	03	04
	No	67	43	64	08	12	08	12	08	12
LDL-C >130 mg/dL	Yes	18	08	44	02	11	04	22	04	22
	No	15	04	27	03	20	02	13	06	40
Total	Yes	86	59	69	06	07	14	16	07	08
	No	82	47	57	11	13	10	12	14	17
Grand total		168	106	63	17	10	24	14	21	13

\*Test for linear trend: LDL-C vs HRT,  $P=0.006$ ; LDL-C vs non-HRT,  $P=0.005$ ; HRT vs non-HRT, not significant ( $P=0.19$ ).

in Table 6, a high triglyceride level (>100 mg/dL) was associated with high coronary artery calcium scores  $\geq 101$ , primarily for women with an LDL-C  $\geq 130$  mg/dL. For women with an LDL-C <130 mg/dL, there was little association with triglyceride levels and coronary artery calcification or high coronary calcium scores.

The level of apoB (Tables 2 and 3) was strongly related to the extent of both coronary and aortic calcification. The sample size was not large enough to determine whether apoB levels were a better predictor of coronary and aortic calcification compared with LDL-C levels.

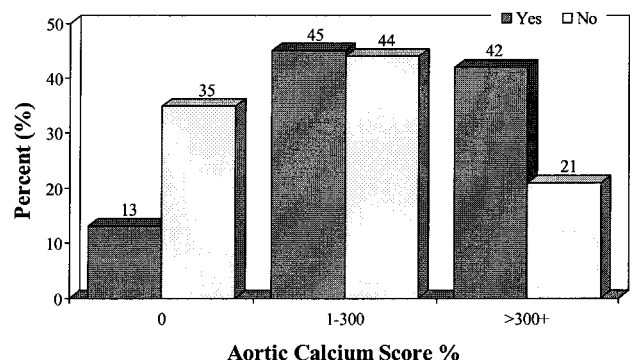
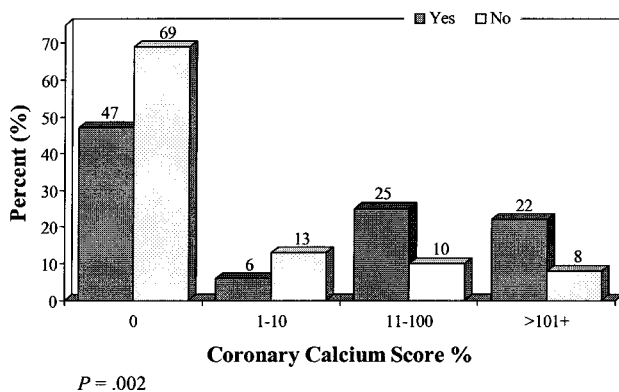
**BMI and Waist Circumference**

There was only a weak association between baseline BMI and aortic or coronary calcification (Tables 2 and 3). Among women with a BMI <25 kg/m<sup>2</sup> (n=108), 12% had high calcium scores  $\geq 101$  and 67% had calcium scores of zero (not shown). There were 45 women with a BMI between 25 and 30 kg/m<sup>2</sup>: 11% had coronary calcium scores  $\geq 101$  and 68% had zero calcium scores, very similar to the results for women with a BMI <25 kg/m<sup>2</sup>. However, for the 17 women with a BMI  $\geq 30$  kg/m<sup>2</sup>, only 29% had zero calcium scores and 18% had high calcium scores  $\geq 101$ . The weak association between BMI and coronary calcium scores could have been confounded by cigarette smoking status. There was no

significant association of coronary or aortic calcification and level of BMI for non-cigarette smokers at the baseline examination. The distribution of BMI by smoking status was also similar (ie, smokers and nonsmokers had a similar distribution of BMI). The study initially excluded women who were having abnormal menstrual periods and who were hypertensive or diabetic and therefore may have excluded women at higher risk associated with BMI.

The association between baseline BMI and aortic scores was even weaker than that for coronary calcification. Twenty-five percent of women with a BMI <25, 28% with a BMI between 25 and 30, and 33% with a BMI >30 kg/m<sup>2</sup> had aortic calcium scores  $\geq 300$  (not significant). Neither supra-iliac nor triceps skinfold, as measured at baseline, was associated with greater coronary or aortic calcium scores.

The waist circumference was not evaluated in 1983 to 1984 for most of the women in the study. At the first postmenopausal examination, however, waist circumference was added and waist-hip ratio was also calculated. This first postmenopausal waist circumference was very strongly related to coronary calcium scores ( $P=0.004$ ) but less strongly to aortic scores ( $P=0.07$ ). Only 27% of the women with a waist circumference <80 cm had any coronary calcium compared with 71% of women with a waist circumference >88 cm. The first postmenopausal BMI was significantly related to coro-



**Figure 5.** Baseline cigarette smoking by coronary and aortic calcium score at eighth postmenopausal examination.

**TABLE 5. Baseline Risk Groups and Coronary Calcium Scores at Eighth Postmenopausal Examination: Distribution of Risk Group**

	LDL-C	HDL-C	n	%	Coronary Calcium Present	
					n	%
Smoker	<130mg/dL	<60mg/dL	21	13	09	43
		>60mg/dL	13	08	05	38
	>130mg/dL	<60mg/dL	10	06	09	90
		>60mg/dL	03	02	01	32
Nonsmoker	<130mg/dL	<60mg/dL	45	27	16	36
		>60mg/dL	56	33	11	20
	>130mg/dL	<60mg/dL	14	08	10	71
		>60mg/dL	06	03	01	16
Total			169	100		

nary calcium scores ( $P=0.01$ ) but only weakly to aortic calcium scores ( $P=NS$ ).

**ApoE Genotype**

Participants in the HWS with the apoE4 genotype had higher LDL-C levels both before and after menopause. For example, in the current sample, the baseline LDL-C was 86 mg/dL for women with the apoE 3-2 genotype, 111 mg/dL for those with apoE 3-3, and 117 mg/dL for those with apoE 4-3 ( $P=0.006$  for linear trends).<sup>25</sup> We found a positive but nonsignificant association between the apoE 4 genotype and coronary calcification: 4.5% of those with 3-2 ( $n=22$ ), 11.5% ( $n=113$ ) with 3-3, and 21% ( $n=29$ ) with 4-3 had coronary calcium scores  $\geq 101$ . The association between apoE genotype and coronary calcification, however, was confounded by the use of HRT. For women who were not taking HRT, there was a strong, significant association between apoE genotype and coronary calcium scores: 92% of those with 3-2 ( $n=12$ ), 57% of those with 3-3 ( $n=51$ ), and only 33% ( $n=15$ ) of those with 4-3 had no coronary calcium ( $P=0.04$ ). There was no association of coronary calcium score and apoE genotype for women on HRT. The largest difference between HRT users and non-HRT users in extent of coronary calcium was for women with an apoE 4 genotype. These results are based on a small sample size but suggest the potential interaction between apoE genotype and HRT.

**Other Risk Factors**

Exercise and alcohol intake were both related to higher HDL-C and HDL<sub>2</sub>-C in the HWS.<sup>26</sup> There was, however, no significant association between the baseline exercise levels and either aortic or coronary calcification. The alcohol consumption of women was low. There was also no relationship between alcohol consumption and either coronary or aortic calcification. These results were similar for women on and not on HRT. Neither the presence of thyroid antibodies nor thyroid-stimulating hormone levels were related to coronary or aortic calcification.

**Multiple Logistic Regression Analysis**

We performed an exploratory multiple logistic regression analysis of the determinants of a high calcium score  $\geq 101$  and a second analysis for a high aortic calcium score  $\geq 300$ . The sample sizes were relatively small. Only 21 of the women had coronary calcium scores  $\geq 101$  and 38 women with an aortic calcium score  $\geq 300$ . Therefore, the confidence interval around the point estimates are very wide.

In the multiple logistic regression analysis for coronary calcification, the OR for a 20-mg/dL increase in LDL-C was 1.42 (95% CI, 0.98 to 2.1); for an HDL-C increase of 10 mg/dL, 0.53 (95% CI, 0.03 to 0.93); for a 10-mm Hg increase in systolic blood pressure, 1.39 (95% CI, 0.86 to 2.3); and for smokers versus nonsmokers, 2.23 (95% CI, 0.71 to 7.0).

**TABLE 6. Relationship of Triglycerides, Baseline LDL-C, and Coronary Artery Calcification\* Among Women With an HDL-C <60 mg/dL at Baseline Examination**

	Triglycerides, mg/dL	n	Coronary Calcification, %			
			0	1-10	11-100	101+
LDL-C <130 mg/dL	<100	53	64	11	13	11
	>100	13	54	08	23	15
LDL-C >130 mg/dL	<100	08	13	25	37	25
	>100	16	25	19	13	44
Triglycerides (all women)	<100	135	69	09	13	09
	>100	33	39	15	18	27

\*There were only 4 individuals with an HDL-C >60 mg/dL who had coronary calcification scores >101; all had triglycerides <100 mg/dL; only 4 participants with an HDL-C >60 mg/dL had triglycerides >100 mg/dL.

None of the other variables such as waist circumference, BMI, triglycerides, or glucose contributed to the risk prediction. The combination of these 4 variables (ie, a 20-mg/dL increase in LDL-C, a 10-mg/dL decrease in HDL-C, a 10-mm Hg increase in systolic blood pressure, and being a cigarette smoker) was associated with an  $\approx 8.5$ -fold increased risk of having a coronary calcium score  $\geq 101$ .

For an aortic calcification score  $>300$ , a 20-mg/dL increase in LDL-C was associated with an OR of 1.33 (95% CI, 0.98 to 1.8); a 10-mg/dL increase in HDL-C with an OR of 0.70 (95% CI, 0.47 to 1.0); a 10-mm Hg increase in systolic blood pressure with an OR of 1.54 (95% CI, 0.99 to 2.4); and smoking with an OR of 1.87 (95% CI, 0.72 to 4.8). Again, none of the other risk factors contributed to risk predictions. The combination of these 4 risk factors was associated with a relative risk of having a high aortic calcium score  $\geq 300$  of  $\approx 5.4$ -fold.

### Discussion

The present report is 1 of the few longitudinal analyses of the relationships between risk factors and coronary calcification based on EBCT. It is the first study to evaluate the relationship of the risk factors measured premenopausally to the extent of subclinical disease in the coronary arteries measure by EBCT among postmenopausal women. The results are striking. LDL-C levels were a powerful predictor of the extent of coronary and aortic calcification. An HDL-C  $>60$  mg/dL resulted in virtual immunity to the development of significant coronary or aortic coronary calcification. Cigarette smoking among premenopausal women was a powerful predictor of aortic and coronary calcification, especially in combination with an LDL-C level  $>130$  mg/dL. Other key risk factors, such as systolic blood pressure, triglyceride levels, and waist circumference, were also determinants of the extent of coronary and aortic calcification in this longitudinal analysis.

The relationship of the risk factors, especially LDL-C, to the extent of coronary and aortic calcification is modified by HRT. Women on HRT at their eighth postmenopausal examination, many of whom had been on long-term HRT since their first postmenopausal visit, had a lower prevalence of extensive coronary calcification, ie, a score  $\geq 101$ . The relationship between HRT use and subsequent coronary calcification was strongly related to the LDL-C levels at premenopause. Only 4% of women with a baseline premenopausal LDL-C  $<130$  mg/dL and on HRT had coronary calcium scores  $\geq 101$  compared with 22% of women on HRT with an LDL-C  $>130$  mg/dL. Similarly, women not on HRT with an LDL-C  $<130$  mg/dL had only a 12% prevalence of high coronary calcium (ie, score  $\geq 101$ ) compared with 40% of women who were not on HRT and who had an LDL-C  $>130$  mg/dL. The majority of women (68 of the 86, or 79%) on HRT had LDL-C levels  $<130$  mg/dL at baseline before therapy and were "at low risk."

Only 4% of the women on HRT and 6% of women not on HRT with an HDL-C  $>60$  mg/dL at the premenopausal visit had coronary calcium scores  $\geq 101$ . Yet again, 46 (53%) of the 86 women on HRT would be considered to be at very low risk (HDL-C  $>60$  mg/dL). There was little evidence that the selection for HRT was in any way related to the premeno-

pausal cardiovascular risk status, except for a lower prevalence of cigarette smoking among HRT-treated women.

The combination of LDL-C and HDL-C identified groups of women with a  $>9$ -fold difference in the risk of high calcium scores and an almost 4-fold difference in the likelihood of having no coronary calcium at all. Women with an LDL-C  $>130$  and an HDL-C  $<60$  mg/dL were at high risk (38% risk of having high calcium scores  $\geq 101$ ) versus only 4% for those with an LDL-C  $<130$  and an HDL-C  $>60$  mg/dL. However, of the 21 women (13%) with high calcium scores in their coronary arteries, only 9 of 21 (43%) were in the high-risk category and an equal number, 8 of 21 (38%), had an LDL-C  $<130$  and an HDL-C  $<60$  mg/dL. Thus, including only the high-risk women (ie, based on LDL-C and HDL-C) for further evaluation and treatment would miss more than half of the high-risk women. Similarly, 10 of the 24 (42%) high-risk (ie, LDL-C  $>130$  or HDL-C  $<60$  mg/dL) had very low coronary calcium scores, approximately the same as the number of women who had very high calcium scores. Treatment decisions such as lipid-lowering therapy based only on LDL-C and HDL-C levels during premenopause (even though there was a very high relative risk) would result in exclusion of the majority of women who subsequently had high coronary calcium scores and the inclusion of many women who had minimal or no risk of high coronary calcium scores.

The addition of cigarette smoking to a model enhances its predictive power. Among smokers with an LDL-C  $>130$  and an HDL-C  $<60$  mg/dL, 86% had evidence of any coronary calcification compared with only 17% of women who were nonsmokers with an LDL-C  $<130$  and an HDL-C  $>60$  mg/dL. However, only 28% of the women were cigarette smokers at the baseline examination. Including only cigarette smokers with high LDL-Cs and low HDL-Cs identifies a small but very-high-risk group of women but misses the majority of women with any degree of coronary calcification. Thus, of the 63 women who had any coronary calcification, only 8 of them (12%) were in this higher-risk category, ie, smokers with an LDL-C  $>130$  and an HDL-C  $<60$  mg/dL, although their relative risk of calcification compared with nonsmokers with an LDL-C  $<130$  and an HDL-C  $>60$  mg/dL was  $\approx 5$ -fold.

There was a very high correlation between coronary and aortic calcium scores. The aortic calcium scores were higher than those for the coronary arteries. Among the women with zero coronary calcium scores, only 37% also had a zero aortic score; 49% had an aortic score of 1 to 300, and 14% had a score  $>300$ . Previous pathology studies have shown that the sex difference for aortic atherosclerosis is much smaller than for coronary atherosclerosis and that aortic disease may begin earlier than coronary atherosclerosis. The risk factors for both coronary and aortic atherosclerosis were very similar.<sup>27,28</sup> It is possible that aortic calcification develops before coronary calcification among these women. Measures of aortic calcification by EBCT may be useful for identifying women, even in the premenopause, who are likely to subsequently develop high amounts of coronary calcification and coronary atherosclerosis and therefore are at increased risk of clinical coronary heart disease.

A large number of high-risk women in this study (based on their elevated risk factors) had minimal calcification in their

coronary arteries and aorta. It is possible that some of these women did have calcification in the aorta, earlier disease, or noncalcified but extensive atherosclerotic disease. The HWS also included measures of carotid intima-media thickness and plaque index.<sup>22</sup> A high plaque index or wall thickness might be an indicator of noncalcified atherosclerotic disease.

We first evaluated whether the women with an LDL-C >130 mg/dL and a coronary calcium score of zero had any evidence of calcification in the aorta. Of the 12 women in this category with aortic measurements, only 1 had an aortic calcium score >300 compared with 9 of 10 women with an LDL-C >130 mg/dL and a coronary calcium score  $\geq$ 101. Only 2 of the 12 women with an LDL-C >130 mg/dL and a zero calcium score had a carotid plaque index >2 compared with 6 of 9 women with an LDL-C >130 mg/dL and a calcium score  $\geq$ 101. Also, only 2 of these 12 women were in the top quartile of carotid intima-media thickness. The women with high LDL-Cs (>130 mg/dL) and zero calcium scores in the coronary arteries had a low overall prevalence of subclinical vascular disease, both carotid and aortic.

We then evaluated the women with an LDL-C <130 mg/dL and coronary calcium scores  $\geq$ 101 (n=11). Five of these 11 were cigarette smokers at baseline examination (Table 5). Ten of these 11 had some aortic calcium and 6 of the 11 (55%) had an aortic calcium score  $\geq$ 300 compared with 13 of 90 women (14%) with an LDL-C <130 mg/dL and zero coronary calcium scores. Four of 10 (40%) had a maximum carotid intima-media thickness in the top quartile compared with 20% of women with an LDL-C <130 mg/dL and a zero coronary calcium score. Surprisingly, only 1 of these 10 women with low LDL-C and a high coronary calcium score had a plaque index of 2 or greater, similar to those with an LDL-C <130 mg/dL and a zero calcium score. These results are based on a small sample size but suggest a possible difference in carotid plaque index and coronary calcium scores, at least for women with an LDL-C <130 mg/dL.

Further evaluation of women with low LDL-C levels and extensive coronary calcification is important, especially with larger sample sizes. These women either may be more "sensitive" to lower LDL-C levels or have other risk factors that contribute to the development of coronary atherosclerosis. They would probably be missed by current risk stratification.

An important issue is whether coronary calcification or extensive atherosclerosis is an important determinant of coronary heart disease among women. There is solid evidence that women who die suddenly due to coronary heart disease or after a myocardial infarction have extensive coronary atherosclerosis. We previously evaluated the determinants of sudden cardiovascular death among women 25 to 64 years of age in Allegheny County. Cigarette smoking was a major risk factor for sudden and unexpected death. Sixty-four percent of the women who died suddenly from coronary artery disease without a prior history of heart disease and 26% of the controls were current cigarette smokers. The women who died suddenly had extensive coronary atherosclerosis.<sup>29,30</sup> Of the 42 autopsied deaths, 29 (69%) had either 3 or 4 coronary arteries (left main defined as a separate artery) with >50% occlusion. These results, with regard to the extent of coronary artery disease, were similar to previous studies in the late 1960s and early 1970s in Baltimore, Md. Women who died suddenly due to coronary heart disease usually had extensive coronary atherosclerosis, similar to the situation in men.

Women who have already experienced a myocardial infarction also usually have extensive coronary atherosclerosis, as measured and evaluated by coronary angiography.<sup>29</sup>

The progression of atherosclerosis to clinical disease includes changes in the characteristics of plaque, inflammation, and thrombosis. The study of coronary calcification alone does not provide information about subsequent changes in atherosclerotic plaque characteristics that may lead to clinical disease. In the CHS (Cardiovascular Health Study) and several other epidemiological studies, the assessment of measures of inflammation, thrombosis, and fibrinolysis are being evaluated in association with subclinical disease.<sup>1,31</sup> A recent pathology study, for example, has evaluated the changes in plaque morphology and sudden death among women. Burke et al<sup>32</sup> examined 51 cases of sudden death in women. Thirty of the deaths occurred in women <50 years of age. Acute thrombosis, with the thrombus overlying plaque erosion, was present in 18 of the hearts (35%); with thrombus overlying plaque rupture, in 8 (16%); with a stable plaque and a healed infarct, in 18 (35%); and with a stable plaque and no infarct, in 7 (14%). The number of arterial segments with >50% cross-sectional luminal narrowing was 12 in women older than 50 and 7 in women <50 years of age. The results of these studies clearly demonstrate that premenopausal risk factors are important determinants of the risk of subclinical atherosclerosis as measured by EBCT in postmenopausal women. Therefore, it is possible to identify these women premenopausally to potentially prevent the development of atherosclerosis.

The study also demonstrates that the majority of women (at least in this Pittsburgh study) on HRT were at low risk of either coronary or aortic calcification: most had a low LDL-C and a high HDL-C and were nonsmokers. There was little evidence that selection for HRT was related to their cardiovascular risk status.

Large, longitudinal studies of risk of coronary artery disease have now demonstrated that measures of subclinical disease are independent predictors of clinical coronary artery disease.<sup>5,8,10,12,33</sup> These measures of peripheral atherosclerosis are correlated with coronary calcification on EBCT. It is extremely likely that coronary calcification will be an even stronger predictor of risk of coronary disease as a direct measure of coronary atherosclerosis.

If the risk factors were highly predictive (ie, high relative and attributable risk of atherosclerosis and its surrogate marker, coronary calcification), then measures of subclinical disease could conceivably become less important. This study clearly demonstrates that the risk of a high coronary and aortic calcium score is strongly related to the risk factors. Many individuals with relatively low risk factors have high coronary calcium scores, and some participants with high risk-factor levels (such as high LDL-C or low HDL-C) may have minimal coronary or aortic calcification. The reason for this less-than-perfect association of risk factors and the extent of atherosclerosis is due to variations in host genetic susceptibility, measurement errors of risk factors and of atherosclerosis, and probably other unmeasured risk factors such as oxidized LDL-C, inflammatory markers, adhesion molecules, etc. The use of these subclinical measures provides an important new approach to identify both the interaction of environmental and risk factors and host susceptibility and the possible identification of new risk factors as well as enhancing risk stratification for treatment guidelines.

The availability of very efficacious therapies to reduce the risk of coronary heart disease among women will require improved methods of risk classification to determine the choice of drug therapy, a more aggressive lipid-lowering diet and other lifestyle changes, or a less intensive public health model.<sup>28,34</sup> The measures of subclinical disease in combination with traditional cardiovascular risk factors may provide better algorithms for treatment recommendations, especially with regard to lipid-lowering drug therapy in the primary prevention of cardiovascular disease.

## Appendix

**TABLE 7. Spearman Correlations Between Risk Factors and Coronary and Aortic Calcium Measures**

Baseline Risk Factors	Coronary Calcium		Aortic Calcium	
	<i>R</i>	<i>P</i>	<i>R</i>	<i>P</i>
HDL-C	-0.28	<0.001	-0.25	0.002
HDL <sub>2</sub> -C	-0.31	<0.001	-0.24	0.003
LDL-C	0.21	0.007	0.27	<0.001
ApoB	0.21	0.007	0.12	0.132
Triglycerides	0.22	0.004	0.24	0.003
BMI	0.13	0.092	0.02	0.757
Fasting glucose	-0.01	0.912	0.18	0.027
Systolic blood pressure	0.17	0.028	0.15	0.048
Diastolic blood pressure	0.14	0.076	0.07	0.356

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