

# Coronary and Aortic Calcification in Women With a History of Major Depression

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**Background:** Although depression is a well-documented risk factor for clinical heart disease, its association with subclinical atherosclerosis is unclear. We hypothesized that middle-aged women with a history of recurrent major depression would show evidence of atherosclerosis.

**Methods:** Coronary and aortic calcification was measured by electron beam tomography in 58 African American and 152 white healthy middle-aged women. Women were administered the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and a self-report measure of current depressive symptoms.

**Results:** Coronary calcification was found in 103 women (49%) and aorta calcification in 144 women (54%); high calcification scores were set at approximately 75% of the sample distribution (ie, at  $\geq 10$  for the coronary calcium score [n=49 women] and at  $> 100$  for the aorta calcium score [n=53 women]). Women with a history of recurrent major depression (n=53) were more likely to have any coronary calcification or calcification in the high category at either site compared with women with a his-

tory of a single episode of depression or no depression. After stepwise forward adjustment for cardiovascular risk factors and sociodemographic characteristics, a history of recurrent major depression, compared with a single episode or no history, was associated with odds ratios (ORs) of 2.46 (95% confidence interval [CI], 1.06-5.67) for any coronary calcification, 2.71 (95% CI, 1.08-6.81) for high coronary calcification, and 3.39 (95% CI, 1.34-8.63) for high aortic calcification. Further adjustments for waist-hip ratio reduced the association between history of recurrent depression and any calcification (OR, 2.24; 95% CI, 0.94-5.32) and high calcification (OR, 2.31; 95% CI, 0.89-5.99).

**Conclusions:** In this sample of asymptomatic middle-aged women without known coronary disease, recurrent major depression was independently associated with coronary and aortic calcification. Waist-hip ratio in part mediated the association. Our findings suggest that recurrent major depression may be a risk factor for early atherosclerosis in women.

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**H**IGH LEVELS OF DEPRESSIVE symptoms are a risk factor for recurrent events in those with clinical coronary heart disease (CHD).<sup>1-6</sup> Depressive symptoms may also predict CHD in healthy individuals.<sup>7</sup> The risk persists after control for conventional risk factors, such as smoking, hypertension, and diabetes.<sup>8,9</sup> A recent meta-analysis<sup>10</sup> of 11 studies found that depression, combining studies of depressive symptoms and clinical depression, was associated with the development of CHD in initially healthy patients. Only 3 of the studies addressed the risk associated with clinical depression, with 2 showing a strong effect in men and women combined and the other study showing a weak effect in women.

Whether depression is consequent or antecedent to CHD has been an area of inquiry for some time. The process of athero-

sclerosis begins long before clinical CHD.<sup>11</sup> Assessment of atherosclerosis before clinical events occur helps delineate the temporal relationship of depression and CHD. Detection of precursors of CHD avoids the impact of awareness of heart disease that could provoke a depressive response.

*See also pages 1214  
and 1239*

Several reliable measures are available to measure subclinical atherosclerosis. Electron beam tomography (EBT) is used to evaluate the coronary arteries and aorta by directly measuring calcification in the vessels' walls. Coronary calcification scores are strongly related to the severity of angiographic disease<sup>12</sup> and histiologic atherosclerosis,<sup>13,14</sup> elevated cardiovascular risk factors,<sup>15</sup> and incident CHD.<sup>16-18</sup>

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Studies of depression and subclinical atherosclerosis are few. In a study<sup>19</sup> of predominantly male, healthy US Army personnel, depressive symptoms were not related to coronary calcification. Among patients with type 1 diabetes mellitus, depressive symptoms were associated with calcification in men but not in women.<sup>20</sup> In healthy middle-aged women enrolled in the Study of Women's Health Across the Nation (SWAN),<sup>21</sup> those who had a recurrent history of major depression had twice the risk of carotid plaque compared with participants with a single episode of depression or no history, suggesting that exposure to multiple episodes of depression may lead to early risk for atherosclerosis. (A list of the SWAN Study Investigators appears on page 1234.)

The present study tested the hypothesis that healthy African American and white, middle-aged women with a history of recurrent major depression have a greater risk of coronary artery and aortic calcification compared with women with a single episode or no history of depression. The independent association between lifetime history of recurrent major depression, diagnosed using the nonpatient edition of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (SCID-IV/NP), and calcification was examined while controlling for traditional cardiovascular factors and sociodemographic characteristics.

## METHODS

### PARTICIPANTS

Fifty-eight African American and 152 white women participated in the current study from the Pittsburgh, Pa, site of SWAN. SWAN is a multisite, multiethnic, community-based, longitudinal study designed to study reproductive hormones and a variety of health-related factors as women transition through menopause.<sup>22</sup> SWAN eligibility criteria at study entry were age of 42 to 52 years, at least 1 menstrual period in the prior 3 months, no use of any hormone preparations, an intact uterus and at least 1 ovary, and white or a member of the minority group designated for the site. The primary recruitment strategies at the Pittsburgh site were random-digit dialing and sampling from voter registration lists with a target of recruiting white and African American participants in the ratio of 2:1. Exclusionary criteria for the subclinical cardiovascular disease measurements were reports of prior history of clinical heart disease (ie, history of myocardial infarction, congestive heart failure, angina, intermittent claudication, cerebral ischemia, or revascularization); treated diabetes; use of female hormones in the prior 3 months; current pregnancy; or hysterectomy or bilateral oophorectomy. There were no exclusionary criteria for SCID-IV/NP<sup>23</sup> administration. This report is based on 210 women who participated in the 2 site-specific protocols. This group was drawn from a pool of 280 women who were eligible for the EBT study, with 246 agreeing to participate. A total of 216 women had an EBT evaluation as of September 2003. Of these, 1 refused to participate in the mental health assessment and 5 did not have SCID-IV measurements for all visits before the EBT evaluation. In addition, 22 women who completed both studies did not have complete covariate information and are not included in the multivariate analyses. Participants were healthier at baseline than nonparticipants, with lower blood pressures (systolic,  $P < .001$ ; diastolic,  $P = .01$ ), waist-hip ratios ( $P = .02$ ), and fast-

ing glucose levels ( $P = .01$ ), and were better educated ( $P = .01$ ), white ( $P = .03$ ), and nonsmokers ( $P = .006$ ). No differences occurred in age, body mass index (BMI), triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels. The better health of participants is consistent with the selection criteria for the subclinical disease study.

## PROCEDURES

All SWAN participants are followed up yearly, at which time physiologic and psychological measurements are obtained. Blood samples were obtained at the baseline visit and each subsequent follow-up visit scheduled when possible between days 2 and 5 of the participant's menstrual cycle, if still menstruating, following a 12-hour fast. A history of major depression was diagnosed by using the SCID conducted at baseline and annually to assess participants' mental health before study entry and during the year between annual visits. Beginning at the third annual visit, EBT measures of calcification in the coronary arteries and aorta were obtained. Median time between study entry and EBT was 4.75 years (range, 3.7-6.3 years). Written informed consent was obtained at baseline and at each subsequent follow-up visit, as well as before calcification evaluation. The University of Pittsburgh's institutional review board approved all study protocols, which were conducted in accordance with institutional guidelines.

## CARDIOVASCULAR RISK FACTORS

Anthropometric measurements, including height, weight, waist and hip circumferences, BMI, systolic blood pressure, and diastolic blood pressure, were obtained. A fasting blood sample was drawn to measure total serum cholesterol, total HDL-C, calculated LDL-C, triglycerides, insulin, and glucose levels. All blood samples were maintained at 4°C until prepared for storage, frozen at -70°C, placed on dry ice, and transported to the central laboratory (Medical Research Laboratories, Highland Heights, Ky) for analysis. Throughout the study the laboratory participated in and maintained certification by the Centers for Disease Control and Prevention, National Heart, Lung, and Blood Institute, Lipid Standardization Program.<sup>24</sup> Total cholesterol and triglyceride levels were analyzed using enzymatic methods on a Hitachi 747 analyzer (Boehringer Mannheim Diagnostics, Indianapolis, Ind),<sup>25</sup> and HDL-C was isolated using heparin-manganese.<sup>26</sup> The LDL-C levels were calculated using the Friedewald equation.<sup>27</sup>

Blood pressure was measured by a trained technician with a standard mercury column with cuff size, position, and rest period standardized for each participant. Two blood pressure readings were taken for each participant and averaged for use in the analysis. The BMI was calculated by dividing weight in kilograms by the square of height in meters. Information regarding medical history updates, change in menopausal status from the last visit, health behaviors, and sociodemographic factors was obtained. Menopausal status was defined according to bleeding patterns as follows: premenopause (menstrual period in the past 3 months and no decrease in predictability in the preceding 12 months), early perimenopause (menstrual period in the past 3 months but less predictable in the preceding 12 months), late perimenopause (menstrual period in the past 12 months but not in the past 3), and natural postmenopause (amenorrheic for the past 12 months and no hysterectomy). Cardiovascular data were obtained from the study visit, which corresponded to the EBT measures.

**Table 1. Cardiovascular Risk Factors and Sociodemographic Characteristics According to History of Major Depression\***

Risk Factor	History of Major Depression			P Value	
	None (n = 124)	Single Episode (n = 33)	Recurrent (n = 53)	None or Single vs Recurrent	None vs Single
Age at scan, y	51.0 (2.6)	50.8 (2.8)	50.5 (3.1)	.32	.69
African American, No. (%)	33 (27)	10 (30)	15 (28)	.90	.67
College or higher, No. (%)	49 (40)	14 (44)	30 (58)	.03	.66
SBP, mm Hg	112.3 (15.4)	114.6 (13.7)	115.4 (18.1)	.30	.46
DBP, mm Hg	72.0 (10.7)	75.0 (8.7)	74.7 (11.4)	.23	.14
BMI	28.3 (5.9)	28.7 (5.2)	30.1 (7.1)	.09	.74
Waist-hip ratio	0.81 (0.07)	0.82 (0.07)	0.84 (0.09)	.02	.61
Triglycerides, mg/dL	125.7 (117.2)	110.1 (60.0)	148.1 (108.8)	.08	.43
LDL-C, mg/dL	122.1 (33.2)	123.4 (35.6)	128.0 (37.1)	.32	.85
HDL-C, mg/dL	58.7 (14.4)	63.4 (14.6)	55.9 (16.3)	.12	.11
Fasting glucose, mg/dL	88.2 (9.3)	87.6 (8.7)	98.7 (31.9)	<.001	.75
Smoker, No. (% of group)	18 (15)	3 (9)	8 (15)	.77	.57
Coronary calcium, median (IQR)	0 (0-6.0)	0 (0-2.4)	4.5 (0-17.5)	.006	.26
Aorta calcium, median (IQR)	15 (0-80.5)	15 (0-55)	30 (1.2-219)	.06	.43

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

SI conversion factors: To convert triglycerides to millimoles per liter, multiply by 0.0113; LDL-C and HDL-C to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

\*Data are given as mean (SD) unless otherwise specified. Comparisons of triglycerides and glucose were based on log-transformed scores. P values were obtained by Kruskal-Wallis test.

**Table 2. Bivariate Associations Between Cardiovascular Risk Factors and Coronary Calcification Groups\***

Risk Factor	Coronary Calcium Score			P Value	
	0 (n = 107)	1-9 (n = 54)	≥10 (n = 49)	0 vs >0 Score	<10 vs ≥10 Score
Age at scan, y	50.5 (2.7)	50.6 (2.8)	51.8 (2.6)	.10	.004
African American, No. (%)	23 (22)	22 (41)	13 (26)	.04	.85
College or higher, No. (%)	51 (48)	21 (40)	21 (43)	.32	.77
SBP, mm Hg	107.9 (13.3)	120.0 (19.7)	118.8 (11.7)	<.001	.007
DBP, mm Hg	69.7 (8.7)	77.9 (13.8)	75.6 (7.6)	<.001	.07
BMI	25.5 (3.7)	31.0 (4.5)	33.8 (7.7)	<.001	<.001
Waist-hip ratio	0.79 (0.06)	0.83 (0.07)	0.86 (0.08)	<.001	<.001
Triglycerides, mg/dL	108.6 (67.4)	131.7 (96.2)	174.3 (171.0)	<.001	<.001
LDL-C, mg/dL	118.1 (33.5)	131.9 (36.7)	128.1 (32.6)	.02	.35
HDL-C, mg/dL	62.0 (16.2)	57.9 (12.8)	52.2 (12.3)	<.001	<.001
Fasting glucose, mg/dL	87.1 (9.3)	92.5 (12.4)	97.6 (33.2)	.01	.007
Smoker, No. (%)	15 (14)	6 (11)	8 (16)	.95	.57

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

SI conversion factors: To convert triglycerides to millimoles per liter, multiply by 0.0113; LDL-C and HDL-C to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

\*Data are given as mean (SD) unless otherwise specified. Comparisons of triglycerides and glucose were based on log-transformed scores. P values were obtained by Kruskal-Wallis test.

## CORONARY AND AORTIC CALCIFICATION

Beginning in 2000, a computed tomography scanner (C-150 Ultrafast CT Scanner; GE Imatron, San Francisco, Calif) was used to quantify calcification in both the coronary arteries and aorta. Three passes were performed: the first allowed an evaluation of the patient's anatomy so that the landmarks for the coronary and aortic scans could be identified. The second pass was for the coronary arteries, in which 30 to 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 a maximal breath hold using electrocardiographic triggering so each 100-millisecond

exposure was obtained during the same phase of the cardiac cycle (60% of the R-R interval). The third pass was for the aortic evaluation. The scanner was set to acquire images from the aortic arch to the iliac bifurcation, and cross-sectional 6-mm images were taken with a 300-millisecond exposure time. The scanner was set in CVA mode so that gating was not required. The participant was again asked to hold her breath during this time. All scan data were saved to an optical disk for central scoring using a DICOM workstation and software by AcuImage, Inc (South San Francisco, Calif). This software program implements the Agatston scoring method.<sup>28</sup> Coronary artery and aortic calcium lesions were considered to be present when 3 contiguous pixels

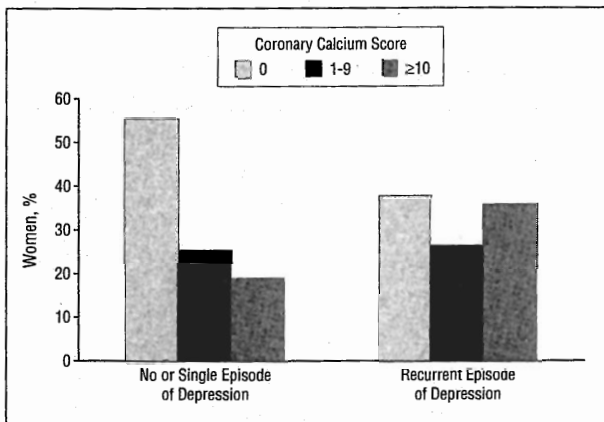
**Table 3. Bivariate Associations Between Cardiovascular Risk Factors and Aortic Calcification Group\***

Risk Factor	Aorta Calcium Score				P Value	
	0 (n = 66)	1-20 (n = 43)	21-100 (n = 48)	>100 (n = 53)	0 vs >0 Score	≤100 vs >100 Score
Age at scan, y	50.4 (2.8)	50.4 (2.9)	51.0 (2.5)	51.6 (2.7)	.10	.02
African American, No. (%)	12 (18)	18 (42)	16 (33)	12 (23)	.04	.35
College or higher, No. (%)	31 (48)	21 (50)	22 (46)	19 (36)	.56	.13
SBP, mm Hg	106.9 (14.7)	112.3 (9.9)	116.4 (18.2)	120.2 (16.1)	<.001	<.001
DBP, mm Hg	70.1 (9.2)	72.3 (7.7)	75.5 (12.0)	75.7 (12.1)	.004	.05
BMI	24.4 (2.6)	28.6 (3.3)	30.8 (5.3)	33.0 (8.1)	<.001	<.001
Waist-hip ratio	0.77 (0.05)	0.82 (0.06)	0.83 (0.07)	0.86 (0.08)	<.001	<.001
Triglycerides, mg/dL	89.0 (37.4)	112.4 (62.1)	126.0 (70.0)	198.9 (178.8)	<.001	<.001
LDL-C, mg/dL	112.8 (25.9)	122.5 (28.4)	127.2 (35.9)	136.9 (43.3)	.002	.003
HDL-C, mg/dL	63.8 (15.4)	61.3 (13.5)	58.0 (15.4)	50.7 (12.1)	<.001	<.001
Fasting glucose, mg/dL	86.3 (7.8)	87.4 (8.7)	91.5 (8.4)	99.1 (33.3)	.005	<.001
Current smoker, No. (%)	5 (8)	6 (14)	6 (12)	12 (23)	.07	.03

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

SI conversion factors: To convert triglycerides to millimoles per liter, multiply by 0.0113; LDL-C and HDL-C to millimoles per liter, multiply by 0.0259; glucose to millimoles per liter, multiply by 0.0555.

\*Data are given as mean (SD) unless otherwise specified. Comparisons of triglycerides and glucose were based on log-transformed scores. P values were obtained by Kruskal-Wallis test.



**Figure 1.** Proportion of women in each level of the coronary calcification group within women with recurrent episodes of depression and women with no or a single episode of depression.

greater than 130 Hounsfield units were detected overlying the vessels of interest. Scoring resulted in a total calcium score, total calcium volume score, and total number of calcium lesions. Total calcium score and total volume score were highly correlated ( $r=0.99$ ). For this study's analyses, the total calcium score that is widely reported in the literature was used. The coronary calcium score was obtained from the sum of the individual scores for the 4 major epicardial coronary arteries. Aortic calcification produced one score. Under the supervision of a cardiologist, a technologist unaware of the depressive state of the participants scored the scans.

### DEPRESSION ASSESSMENTS

The SCID-IV/NP<sup>23</sup> is a semistructured diagnostic interview designed to enable a trained clinician to make current and lifetime diagnoses according to the criteria listed in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.<sup>29</sup> The sections on mood disorders, anxiety disorders, and alcohol and substance abuse were administered at the baseline visit and each subsequent visit to obtain informa-

tion on any new diagnoses that had occurred since the prior study visit. The SCID-IV interviewers were trained clinicians with an MD or PhD degree, a master's degree in psychology, social work, or a related field, or a degree in psychiatric nursing. Interviewers completed a multistep certification process, including a training session with a Biometric Institute member, review of videotaped practice interviews by one of the authors (J.T.B.), and review and certification of the videotape by the Biometrics Institute. The diagnosis of recurrent major depression or single episode or none as of the third annual visit was the major independent variable of this study.

The Center for Epidemiological Studies Depression Scale, a 20-item depression symptom scale,<sup>30</sup> was used to assess depressive symptoms in the prior 7 days. Responses ranged from 0 (rarely or none of the time) to 3 (most of the time) and were summed across the 20 items. The Center for Epidemiological Studies Depression Scale scores were examined as a dichotomous variable, with a cutoff of 16 or higher, to identify potential clinically significant symptoms of depression.

### STATISTICAL ANALYSIS

Analyses of variance (ANOVAs) and  $\chi^2$  tests were conducted to compare the risk factor levels of women with a history of at least 2 episodes of depression to the remaining women and of women with a single episode of depression to women with no depression. Coronary and aortic calcium scores were positively skewed, with many women having scores of 0 (51% and 33%, respectively). No established guidelines exist regarding the clinical significance of low calcium scores, so categories were established that corresponded to approximately the top 25% of the distribution. Coronary calcium scores ranged from 0 to 295, with a median of 0, and were separated into 3 groups: 0, 1 through 9, and 10 or greater. Aorta calcium scores ranged from 0 to 2810, with a median of 17, and were divided into 4 groups: 0, 1 through 20, 21 through 100, and 100 or higher. ANOVAs and  $\chi^2$  tests compared the risk factor levels and recurrent depression history of women with no calcium vs women with any calcium and women in the highest category of calcification with the remaining women. Because

**Table 4. Stepwise Logistic Regression Analysis of History of Recurrent Major Depression and Cardiovascular Risk Factors With Calcification of the Aorta and Coronary Arteries\***

Variable	OR (95% CI)		
	Coronary Calcium Score >0 (n = 188; 88 Coronary Calcium Score >0)	Coronary Calcium Score ≥10 (n = 188; 43 Coronary Calcium Score ≥10)	Aorta Calcium Score >100 (n = 188; 44 Aorta Calcium Score >100)
Age at scan	1.12 (0.98-1.29) (P = .10)	1.27 (1.08-1.50) (P = .004)	1.12 (0.95-1.32) (P = .17)
African American	1.48 (0.65-3.37) (P = .35)	0.85 (0.32-2.27) (P = .75)	0.34 (0.11-1.02) (P = .05)
College or higher	0.81 (0.40-1.67) (P = .57)	0.83 (0.36-1.94) (P = .67)	0.47 (0.19-1.17) (P = .10)
BMI	1.29 (1.19-1.40) (P < .001)	1.21 (1.13-1.31) (P < .001)	1.17 (1.08-1.26) (P < .001)
Triglycerides	NA	NA	3.47 (1.43-8.41) (P = .006)
Current smoker	NA	NA	7.74 (2.58-23.21) (P < .001)
History of recurrent major depression	2.46 (1.06-5.67) (P = .04)	2.71 (1.08-6.81) (P = .03)	3.39 (1.34-8.63) (P = .01)

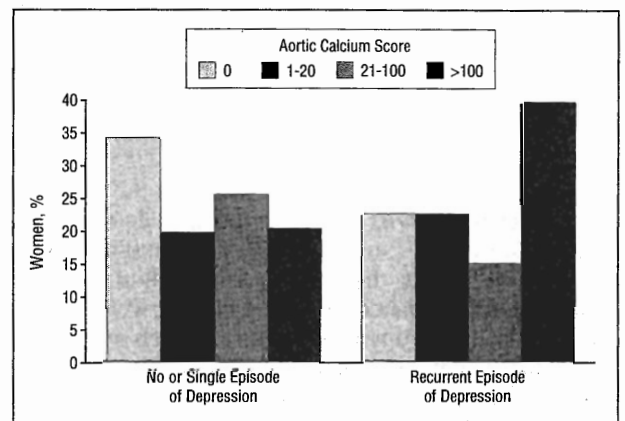
Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); CI, confidence interval; NA, not applicable (variables that did not enter the model and variables not included in the table did not enter the model after adjustment for other covariates); OR, odds ratio. \*Age, ethnicity, and education were forced into the model, followed by stepwise selection of blood pressure, BMI, log-triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, log-glucose, and smoking, followed by recurrent depression. Model diagnostics: coronary calcium score greater than 0 (generalized  $R^2 = 0.43$ , Hosmer and Lemeshow goodness-of-fit test  $\chi^2_8 = 6.32$ ,  $P = .61$ ); coronary calcium score of 10 or higher (generalized  $R^2 = 0.39$ , Hosmer and Lemeshow goodness-of-fit test  $\chi^2_8 = 7.14$ ,  $P = .52$ ); aorta calcium score greater than 100 (generalized  $R^2 = 0.41$ , Hosmer and Lemeshow goodness-of-fit test  $\chi^2_8 = 12.35$ ,  $P = .13$ ).

of multicollinearity of the cardiovascular risk factors, stepwise logistic regression analyses that predicted coronary and aortic calcification groups (ie, any vs none, highest calcification group vs others) were conducted in which age, ethnicity, and education were forced in the first step; the risk factors associated with calcification in the univariate analyses were allowed to enter in order of significance thereafter, and finally depression history was allowed to enter the model. The BMI and waist-hip ratio were highly correlated ( $r=0.56$ ), so models were conducted with BMI only, and the waist-hip ratio was allowed to enter if significantly independent of BMI. The BMI was given primacy because of the association of body weight and soft tissue attenuation.<sup>31</sup> Ordinal multinomial regression could not be used, because it violated the proportional odds assumption. Statistical significance was accepted at  $P \leq .05$  (2-tailed).

## RESULTS

Of the 210 women in the analyses, 53 (25%) met the criteria for history of recurrent major depression. Most participants were white, with the prevalence of major depression comparable in the 2 ethnic groups. Most were perimenopausal (early and late, 63%); menopausal status was unrelated to depression groups. Few women drank alcohol daily. Women who had a history of a single episode of depression and women who had no history of depression were similar in their cardiovascular risk factor levels and educational level and ethnicity (**Table 1**). Women who had a history of recurrent depressive episodes had a higher waist-hip ratio, had a higher fasting glucose level, and were more educated compared with all other women.

Calcification was highly correlated between the 2 sites ( $r=0.55$ ,  $P < .001$ ), and both any coronary and any aortic calcification were found in 45% of the women. Women who had any coronary calcification, compared with those who did not, had higher blood pressure, BMI, waist-hip ratio, and triglyceride, LDL-C, and fasting glucose levels and lower HDL-C levels (**Table 2**). Diastolic blood



**Figure 2.** Proportion of women in each level of the aortic calcification group within women with recurrent episodes of depression and women with no or a single episode of depression.

pressure and LDL-C level did not differ between women in the highest-risk coronary calcification group and the remaining women. The analyses that compared groups with any or the highest aortic calcification with the remaining women showed similar risk factor differences, except that smoking status distinguished the aortic calcification groups (**Table 3**). African American participants were more likely to have any calcification in the coronary or aorta than white participants but were not more likely to be in the high calcification groups (Tables 2 and 3). Elevated depressive symptoms tended to be associated with having any coronary calcification vs none (14.6% vs 6.5%, respectively,  $P = .06$ ) but not with having any aortic calcification or being in the high calcification group. Menopausal status was not associated with calcification at either site.

Among women with a history of recurrent depression, the proportion of women with any calcification in the coronary arteries was greater than among the remain-

## SWAN Study Investigators

### Clinical Centers

University of Michigan, Ann Arbor: Mary Fran Sowers, PhD, principal investigator (PI) (U01 NR04061); Massachusetts General Hospital, Boston: Robert Neer, MD, PI 1995-1999; Joel Finkelstein, MD, PI 1999-present (U01 AG012531); Rush University, Rush-Presbyterian-St Luke's Medical Center, Chicago, Ill: Lynda Powell, PhD, PI (U01 AG012505); University of California, Davis/Kaiser: Ellen Gold, PhD, PI (U01 AG012554); University of California, Los Angeles: Gail Greendale, MD, PI (U01 AG012539); University of Medicine and Dentistry, New Jersey Medical School, Newark: Gerson Weiss, MD, PI 1995-2004 (U01 AG012535); Nanette Santoro, MD, PI 2004-present; and the University of Pittsburgh, Pittsburgh, Pa: Karen Matthews, PhD, PI (U01 AG012546).

### National Institutes of Health Program Offices

National Institute on Aging, Bethesda, Md: Marcia Ory, PhD, 1994-2001; Sherry Sherman, PhD, 1994-present; National Institute of Nursing Research, Bethesda, Md: Carole Hudgings, PhD, 1997-2002; Janice Phillips, PhD, 2002-2004; Yvonne Bryan, PhD, 2004-present.

### Central Laboratory

University of Michigan, Ann Arbor: Rees Midgley, PhD, PI 1995-2000; Daniel McConnell, PhD, 2000-present (U01 AG012495), Central Ligand Assay Satellite Services.

### Coordinating Center

New England Research Institutes, Watertown, Mass: Sonja McKinlay, PhD, PI 1995-2001 (U01 AG012553); University of Pittsburgh, Pittsburgh, Pa: Kim Sutton-Tyrrell, DrPH, PI 2001-present (U01 AG012546).

### Steering Committee

Chris Gallagher, MD, chair 1995-1997; Jenny Kelsey, PhD, chair 1997-2002; Susan Johnson, MD, chair 2002-present.

ing women with either a single or no episode of depression (62% vs 45%,  $P=.03$ , **Figure 1**); a similar pattern was obtained among the women in the highest coronary calcium group compared with the remaining women (36% vs 19%,  $P=.01$ ). Women with recurrent depression had more than double the odds of having any coronary calcification or being in the high coronary calcification group compared with the remaining women in the stepwise multivariate analyses that adjusted for age, race, education, and BMI (**Table 4**). The  $R^2$  for the model that predicted any calcification changed from 0.40 to 0.43 when recurrent depression was added and changed for the model that predicted being in the high coronary calcification group from 0.34 to 0.37. The models that allowed waist-hip ratio to enter in addition to BMI showed that recurrent depression approached conventional levels of significance for any coronary calcification (odds ratio [OR], 2.24; 95% confidence interval [CI], 0.94-5.32;  $R^2=0.46$ ) and for high coronary calcification (OR, 2.31; 95% CI, 0.89-5.99;  $R^2=0.39$ ).

The proportion of women in the high aortic calcification category was greater among women with a history of recurrent depression than the remaining women (40% vs 20%,  $P=.005$ , **Figure 2**). Women with recurrent depression were 3 times more likely to be in the high aortic calcification group compared with the remaining women in stepwise multivariate analyses that adjusted for age, race, education, BMI, triglyceride level, and smoking status (Table 4). Allowing waist-hip ratio to enter the model did not alter the results. Although all the logistic regression models provided good model fit, we recognize that with the small number categorized in the high-

risk groups, we may not be able to assess the effect of recurrent depression with great precision while controlling for 6 to 7 covariates.

## COMMENT

Middle-aged healthy women with a history of recurrent major depression were at elevated risk of having both coronary and aortic calcification. Women with a history of recurrent depression were 2 to 3 times more likely to be classified in the groups at the highest level of calcification of the coronaries and aorta compared with women with a single episode of depression or no major depression history. The risk persisted after controlling for cardiovascular risk factors and sociodemographic characteristics, although the effects weakened for coronary calcification when waist-hip ratio was added to the models.

Calcification was not associated with concurrent depressive symptoms, a finding consistent with the Rotterdam Study.<sup>32</sup> The Rotterdam Study reported that depressive disorders were related to severe coronary and aortic calcification, but current high levels of depressive symptoms in the absence of depressive disorders were not related. Perhaps early in the natural history of atherosclerosis, elevated depressive symptoms are not a risk factor for subclinical disease, whereas they are in those who already have coronary disease. It may also be that recurrent depressive episodes are associated with calcification risk, because they represent more prolonged exposure to severe depression than do current measures of symptoms.

The study demonstrated a relationship between cardiovascular risk factors and coronary and aortic calcification. Both coronary calcification and aortic calcification were associated with systolic blood pressure, diastolic blood pressure, BMI, waist-hip ratio, and LDL-C, HDL-C, triglyceride, glucose, and insulin levels, and aortic calcification was also associated with current smoking status, findings consistent with prior studies.<sup>15,33</sup> The strongest predictors of calcification were BMI, waist-hip ratio, HDL-C level, triglyceride level, glucose level, and current smoking status. These findings support the validity of the measures of calcification obtained in this study.

A number of pathways may contribute to the link between depression and calcification. Depression may invoke poor eating habits and sedentary behavior and contribute to weight gain and perhaps to central adiposity.<sup>34</sup> Indeed, in the present sample, recurrent depression was associated with elevated waist-hip ratio and fasting glucose levels, and the magnitude of the effect of recurrent depression was reduced when waist-hip ratio was included in the model. Depressive symptoms are also predictive of the development of the metabolic syndrome, as shown in the Healthy Women Study.<sup>35</sup> Individuals with major depression may have significantly higher levels of inflammatory markers, possibly due to increased release by adipose tissue and white blood cells.<sup>34</sup> Last, activation of the hypothalamic-pituitary-adrenal axis in depression and low heart rate variability may contribute to the risk associated with depression.<sup>36,37</sup>

Our results suggest the potential importance of clinical depression in the early development of subclinical atherosclerosis. Cardiovascular disease is the major cause of mortality among US women and often escapes early detection.<sup>38</sup> Further research is needed to understand how the detection of major depression, or history thereof, can affect the development of atherosclerosis and clinical CHD.

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