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Depressive Symptoms are Related to Progression of Coronary Calcium in Midlife Women: The Study of Women's Health Across the Nation (SWAN) Heart Study

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Abstract

Background—Major depression and depressive symptoms are associated with cardiovascular disease (CVD), but the impact of depression on early atherogenesis is less well known, particularly in women and minorities. This study examined whether depressive symptoms are associated with progression of coronary artery calcification (CAC) among women at mid-life.

Methods—The Study of Women's Health Across the Nation (SWAN) is a longitudinal, multi-site study assessing health and psychological factors in mid-life women. An ancillary study (SWAN Heart) evaluated subclinical atherosclerosis in women who reported no history of CVD or diabetes. In 346 women, CAC was measured twice by electron beam computed tomography, an average of 2.3 years apart. Progression, defined as an increase by 10 Agatston units or more, was analyzed using relative risk regression. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression (CES-D) Scale.

Results—Progression of CAC was observed in 67 women (19.1%). Each 1-SD higher CES-D score at baseline related to a 25% increased risk of CAC progression [RR 1.25, CI 1.06–1.47, $p=0.007$], adjusting for age, time between scans, ethnicity, education, menopausal status, and known CVD risk factors. This risk was similar to the risk induced by BMI [RR 1.31, CI 1.11–1.54, $p=0.001$] and systolic blood pressure [RR 1.28, CI 1.06–1.55, $p=0.01$].

Conclusions—Depressive symptoms were independently associated with progression of CAC in this cohort of midlife women. Depressive symptoms may represent a risk factor that is potentially modifiable for early prevention of CVD in women.

Keywords

atherosclerosis; coronary calcium; women; depression; epidemiology

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Disclosures

The authors have no conflicts of interest to disclose.

Introduction

Cardiovascular disease (CVD) is rare in women younger than age 45, but increases substantially over the next 20 years. At least one in two women will develop CVD, and CVD is the most common cause of death among women ¹. Understanding risk factors for CVD might help in its prevention.

Symptoms of depression and major depressive disorder have been identified as potential risk factors for coronary heart disease (CHD) ^{2, 3}. Longitudinal studies have consistently shown that persons with high levels of depressive symptoms, or with a history of major depressive disorders, are more likely to have clinical coronary events than are persons without depression ⁴.

Sub-clinical CVD can be assessed using non-invasive imaging to detect coronary artery calcium (CAC). Prior studies have shown that CAC predicts incident cardiovascular events^{5, 6} and correlates with degree of atherosclerosis found on pathological exam ⁷. Among middle-aged women ^{8–12}, 41% have some CAC (score >0), and these women show an average increase of 13.2 Agatston units over 2 years, an increase that translates into a 3-fold increase in CVD risk ^{13–16}. A recent review found that CAC progression may be a better predictor of future cardiac events than a single assessment of CAC ¹⁷.

Midlife women are particularly vulnerable to depressive mood ¹⁸; the changing hormonal milieu during the menopausal transition contributes to the worsening of the CVD profile ¹⁹ and to increased prevalence of depressive symptoms ²⁰. Depression predicts CVD, independent of this CVD profile ²¹.

Past studies of depression and CAC have been inconsistent. Major depressive disorder has been linked to higher levels of CAC cross-sectionally ^{22, 23} and longitudinally ²⁴, but depressive symptoms have been unrelated cross-sectionally to CAC ^{22, 25–28} except when these symptoms recur ^{24, 29}. There have been no investigations of the relationship between depressive symptoms and progression of CAC.

We hypothesized that depressive symptoms are related to progression of coronary calcium, independent of age, menopausal status, medication for depression, and known CV risk factors. If true, this hypothesis would point to midlife as a key time to identify women with depression and to target these women not only for aggressive risk factor modification but also treatment for depression.

Methods

Study Population and Procedures

The Study of Women's Health Across the Nation (SWAN) is a 7-site multi-ethnic longitudinal study of women transitioning through menopause, featuring ongoing annual interviews. The design of the study has been reported ³⁰. Eligible women were 42–52, not pregnant or breastfeeding, had an intact uterus and at least 1 ovary, and had menstruated within the past 3 months. SWAN Heart is an ancillary study to assess sub-clinical CVD in women from the Chicago and Pittsburgh sites recruited between 2001 and 2003 without history of CVD (n=608). By design, these sites recruited only non-Hispanic white and black women. Coronary calcium (CAC) measurements and depressive symptoms were obtained on 561 women at baseline and CAC measures on 362 of these women at follow-up an average of 2.3 years later. We excluded 13 women with diabetes (glucose > 6.9 mmol/L or on insulin) and 3 women with missing depressive symptom scores, leaving 346 for analysis. Compared to women excluded from the analysis because of a missing follow-up scan,

women in the analytic sample were less likely to be black or post-menopausal, and had lower systolic blood pressure, but they did not differ in any of other descriptors listed in Table 1, including baseline CAC and depressive symptoms. The research protocol was approved by each site's Institutional Review Board; all women provided written informed consent.

Coronary Artery Calcium

Electron beam computed tomography (EBCT) for CAC scoring was performed with 2 passes, the first to provide landmarks and the second to provide coronary artery images. 30–40 contiguous 3-mm-thick transverse images from the level of the aortic root to the apex of the heart were obtained during maximal breath holding with ECG triggering to obtain a 100-millisecond exposure during the same phase of the cardiac cycle (60% of the RR interval). All scans were scored at the University of Pittsburgh with a DICOM workstation and software by AcuImage, Inc (South San Francisco, CA) using the method established by Agatston⁶. Calcification was considered present if at least 3 contiguous pixels showed >130 Hounsfield units. The calcium score was the sum of scores for each of the 4 major epicardial coronary arteries³¹.

Depressive Symptoms and Covariates

Participants completed baseline and annual exams in SWAN, which included questionnaires, anthropometry, and a blood draw, so that sociodemographic factors, and CVD risk factors could be assessed. Depressive symptoms and covariates were assessed at the annual SWAN closest to each participant's first EBCT scan. These scans were performed within 8 months of the annual SWAN visit, and 95% were done within 4 months.

Depressive symptoms were assessed in SWAN with the 20-item Center for Epidemiological Studies Depression Scale (CES-D)³², validated with good test-retest reliability in ethnically diverse samples³³, and used extensively in epidemiological studies³⁴. The 20-item scale measures the frequency of being bothered by depressive symptoms in the previous week on a scale of 0 (rarely) to 3 (most or all of the time). Item responses are summed for a total score (range 0 – 60); higher scores indicate more depressive symptomatology. Medication for depression was adjudicated by a clinical psychiatrist.

Covariates were chosen from the literature based upon the association with CAC. Age, highest educational degree, marital status, smoking status, medication usage, and hormone therapy (HT) were assessed by questionnaire. Menopausal status was assessed by self-reported bleeding criteria as pre-/peri-menopausal or post-menopausal (no menses for at least 12 months). Economic hardship was assessed with one question about how difficult it is to pay for “basics” (i.e. food, housing, medical care), and analyzed as “somewhat or very hard” versus “not hard at all”.

Resting blood pressure was measured with a mercury sphygmomanometer, using an appropriately sized cuff and a standard protocol with at least a 5-minute rest and participants seated. Two sequential blood pressure readings were obtained, two minutes apart, and averaged. Total cholesterol and high-density lipoprotein cholesterol (HDL-C) were analyzed on EDTA-treated plasma using standard methods^{35, 36}.

Data Analysis

A few participants were missing at least one covariate used in this analysis at the SWAN Heart baseline visit. Single variables were missing on at most 8 (2.3%) except for lipids which were missing on 16 (4.6%) women. Smoking and medication use were taken from the year before if they were missing at the SWAN Heart baseline. To estimate missing

continuous covariates such as BMI and blood pressure, we used person-specific linear regression on all measures obtained up to SWAN Heart baseline.

Participant characteristics are reported as mean $\pm$ SD for continuous variables and compared with t-tests between groups using unequal variances where necessary. We report categorical variables as N (%) and compared them between groups with the chi-square test. Calcium scores at baseline had a skewed distribution with about 55% of the scores equal to zero and 20% of the scores at 10 Agatston units or above.

Because of the skewness of the distribution of the change in CAC, we defined progression of CAC as a change in Agatston score >10 , a cutoff previously used to assess significant CAC progression in an asymptomatic population³⁷. Sensitivity analyses revealed that using alternative cut points (such as 5 Agatston units) did not materially alter the risk factor relationships (data not shown). Relative risk regression³⁸ was used to model the probability of CAC progression in the entire cohort, because calcium change > 10 Agatston units was not rare (19% of participants), and so logistic regression might overestimate relative risk. The probability of CAC progression was modeled as a function of covariates using a generalized linear model with log link, normal error distribution, and robust standard error estimates.

To evaluate the relation of depressive symptoms and possible covariates, we calculated Pearson correlations with continuous variables. For binary variables such as race, we used the non-parametric Wilcoxon test. We estimated a basic relative risk regression model adjusted for age, race, and time between scans, followed by a multivariable model constructed via a backward elimination variable selection process. Covariates that were correlated at $p < 0.20$ with either CAC progression or CES-D were included in the initial model. Non-significant covariates were eliminated one-by-one, using a liberal p-value of 0.10, beginning with the least significant variable. Age, time between scans, race, menopausal status, and HT use were included in all models, regardless of their significance. All continuous variables were standardized to z-scores to make their effects comparable. Results from the basic model and the full model were very similar. To investigate the association of CES-D scores with CAC progression independent of baseline CAC, we added an indicator for a positive baseline CAC score to the final model, and also reran this model for the subset of women with CAC present at baseline. The authors had full access to and take full responsibility for the integrity of the data. All statistical analyses were performed with SAS. (SAS version 9.1, SAS Institute, Inc, Cary, NC)

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Results

Table 1 shows the characteristics of the cohort overall and by CAC progression. Average age was 51, 26% were post-menopausal, 11% were using HT, and 32% were black. The average BMI was 29, and 38% were obese (BMI $\geq$ 30). Calcium scores at baseline ranged from 0–311 Agatston units; 154 (44.5%) women had a positive score. The average increase in calcium was 7.3 Agatston units; 1.9 in the women without calcium at baseline, and 14.1 in the women with a positive calcium score at baseline; 20% had an increase of 10 units or more, and these women were older by one year ($p<.05$), significantly heavier, had higher blood pressure, total cholesterol, and triglycerides. Women with a positive calcium score at baseline were more likely to show CAC progression than others (55/154=36% vs. 12/192=6%, $p<0.001$). CES-D scores showed a skewed distribution; 40 women (11.6%) had scores of 16 or above, considered indicative of depression³². CES-D scores were higher in women with CAC progression than in women without progression (8.9 vs. 6.5, $p=0.048$). Table 2 compares CES-D scores for various subgroups. CES-D scores did not differ by race, education, menopausal status, HT use, or medication use for blood pressure or cholesterol. CES-D scores were higher among women who were taking anti-depressant medication, were smokers, unmarried, or experienced economic hardship. HDL-C was significantly negatively associated with CES-D scores ($r=-0.138$, $p=0.01$), but age, BMI, systolic and diastolic blood pressure, LDL-C, total cholesterol, and triglycerides were not (all $|r|<0.05$, $p>0.40$).

Table 3 shows the results of the relative risk regression model relating CES-D scores to CAC progression for all women and for those with CAC > 0 at baseline. Model 1 includes significant baseline predictors for CAC progression (age, BMI, SBP, statin use, education) plus CES-D scores. Each 1 SD increase in CES-D score was associated with a 25% increased risk of CAC progression. Figure 1 depicts the relation of CES-D scores on CAC progression relative to that of known CVD risk factors. The strength of the effect (RR=1.25) was similar to that of BMI (RR=1.31), SBP (RR=1.28), and age (RR=1.32). Model 2 adds baseline CAC to Model 1. Baseline calcium is a very strong predictor of CAC progression (RR=4.68). However, it does not change the estimate of the effect of the CES-D scores (RR=1.26) from that of Model 1. Among the subset of women with CAC present at baseline (Model 3), the relation of CES-D scores with CAC progression was similar to that obtained in the full sample (RR=1.31). In this model, BMI, age, and statin use were no longer related to CAC progression. When women with no CAC at baseline were examined separately (data not shown), CES-D scores were not associated with CAC progression (RR=0.79 95% CI [0.31,2.03], although the limited amount of CAC progression in this subset may limit the power to detect an effect.

Discussion

As hypothesized, we found that CES-D scores were associated with progression of coronary calcium in midlife women, independent of age, race, menopausal status, and known CVD risk factors. Although the observed changes in CAC were clinically significant³⁷, they were fairly small, as one would expect in healthy middle-aged women with a follow-up period of just over 2 years. The magnitude of CAC progression was similar to that reported in younger women in the Coronary Artery Risk Development in Young Adults Study³⁷ as well as older women in the Multi-Ethnic Study of Atherosclerosis free of CV disease¹⁵. Our estimates for the risk of progression due to age, BMI, and systolic blood pressure are very similar to these other two studies.

Our longitudinal analysis showed that women reporting higher CES-D scores at baseline were more likely to have CAC progression over two years. This difference between prior

cross-sectional^{22, 25–28} and the present longitudinal findings implies that CES-D scores are more strongly related to progression of CAC than to the initial development of CAC. As in previous studies, women with baseline CAC were more likely to show CAC progression. The effect of CES-D scores, however, was the same whether or not we adjusted for baseline CAC.

Depressive symptoms have been linked to the development of clinical CVD^{3, 39, 40}. The current investigation adds support to this finding by showing a relationship between depressive symptoms and the worsening of subclinical disease, a precursor of clinical CVD. Depression has been associated with economic hardship in previous studies⁴¹ and in our data. After adjustments for known risk factors, however, education was the only socioeconomic indicator significantly related to CAC progression, and neither economic hardship nor education influenced the association between depressive symptoms and CAC progression.

Depression may lead to adverse health behaviors such as smoking. In our sample, current smokers had higher levels of depressive symptoms, but smoking was not a significant predictor of CAC progression in either univariate or multivariate analyses. Depression may increase the effects of other CVD risk factors to accelerate the progression of atherosclerosis. Although BMI and blood pressure were strongly associated with CAC progression, they were not related to depressive symptoms in our sample of midlife women. Furthermore, the effect of BMI was eliminated in the model adjusting for presence of CAC at baseline.

Limitations of this study should be mentioned. Although many relevant risk factors were assessed and statistically controlled, the possibility of residual confounding cannot be ruled out. Depressive symptoms were self-reported, recalled over 1 week at the SWAN Heart baseline visit. Future research will examine whether repeated reports of elevated depressive symptoms have an even stronger impact on CAC progression than symptoms assessed at one time.

This study has several strengths. It is the first investigation examining depressive symptoms and CAC progression. This community-dwelling cohort of women traversing the menopause is well-characterized and includes a large number of black women. The women are relatively healthy and free of apparent cardiovascular disease. The study used a well-established and validated scale for assessing depressive symptoms.

Finding a link between depressive symptoms and early subclinical atherosclerotic disease in this cohort identifies a potential modifiable risk factor for the early prevention of CHD in women. Therefore, midlife is a key time to identify women with depression and to target these women not only for aggressive risk factor modification but also for treatment for depression. Treating depression may help prevent CAC progression. In our study, women on medication for depression with low CES-D scores (we may consider these women successfully treated for depression) were no more likely to show CAC progression than women not on anti-depressants with the same CES-D scores. Thus, it is important to screen for depressive symptoms at the time of CAC assessment. However, intervention studies are needed to establish whether improved recognition and treatment of depression decreases CAC progression in healthy subjects.

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Appendix

Clinical Centers

University of Michigan, Ann Arbor – MaryFran Sowers, PI; Massachusetts General Hospital, Boston, MA – Joel Finkelstein, PI 1999 – present; Robert Neer, PI 1994 – 1999; Rush University, Rush University Medical Center, Chicago, IL – Howard Kravitz, PI 2009 – present; Lynda Powell, PI 1994 – 2009; University of California, Davis/Kaiser – Ellen Gold, PI; University of California, Los Angeles – Gail Greendale, PI; Albert Einstein College of Medicine, Bronx, NY – Rachel Wildman, PI 2010; Nanette Santoro, PI 2004 – 2010; University of Medicine and Dentistry – New Jersey Medical School, Newark – Gerson Weiss, PI 1994 – 2004; and the University of Pittsburgh, Pittsburgh, PA – Karen Matthews, PI.

NIH Program Office

National Institute on Aging, Bethesda, MD – Sherry Sherman 1994 – present; Marcia Ory 1994 – 2001; National Institute of Nursing Research, Bethesda, MD – Project Officer. Central Laboratory: University of Michigan, Ann Arbor – Daniel McConnell (Central Ligand Assay Satellite Services).

Coordinating Center

New England Research Institutes, Watertown, MA - Sonja McKinlay, PI 1995 – 2001; University of Pittsburgh, Pittsburgh, PA – Kim Sutton-Tyrrell, PI 2001 – present.

Steering Committee

Chris Gallagher, Former Chair; Susan Johnson, Current Chair

Figure 1. Relation of CES-D Scores and Progression of Coronary Calcification Relative to Known CHD Risk Factors (see text for description of modeling).

Table 1

Characteristics of the Cohort at Baseline Overall and by CAC Progression

	CAC Progression (Δ CAC=10+ Agatston units)		
	Total	no	yes
N	346	279	67
Age, years, mean (SD)	50.8 (2.8)	50.6 (2.7)	51.5 (3.1) [†]
Black, N (%)	111	88 (31.5)	23 (34.3)
Economic hardship, N (%)	68 (19.7)	55 (19.7)	13 (19.4)
Unmarried, N (%)	98 (28.3)	81 (29.0)	17 (25.4)
Education $\geq$ HS, N (%)	54 (15.6)	40 (14.3)	14 (20.9)
Post-menopausal, N (%)	91 (26.3)	70 (25.1)	21 (31.3)
Hormone Therapy use, N (%)	39 (11.3)	35 (12.5)	4 (6.0)
Smoker, N (%)	51 (14.7)	41 (14.7)	10 (14.9)
BMI, mean (SD)	29.0 (6.3)	28.1 (5.8)	32.7 (6.9) [*]
SBP mmHg., mean (SD)	117.6	115.8 (14.3)	124.6 (15.6) [*]
DBP mmHg., mean (SD)	75.3 (9.5)	74.2 (9.1)	79.6 (10.1) [*]
Use of blood pressure medication, N (%)	49 (14.2)	36 (12.9)	13 (19.4)
HDL cholesterol, mmol/L, mean (SD)	3.2 (0.8)	3.2 (0.8)	3.1 (0.8)
LDL cholesterol, mmol/L, mean (SD)	3.1 (0.8)	3.0 (0.8)	3.2 (0.8)
Total cholesterol, mmol/L, mean (SD)	5.1 (1.0)	5.1 (0.9)	5.4 (1.0) [†]
Triglycerides, mmol/L, mean (SD)	1.3 (0.7)	1.2 (0.6)	1.5 (0.9) [†]
Statin [‡] use, N (%)	16 (4.6)	10 (3.6)	6 (9.0) [§]
Presence of any CAC at baseline, N (%)	154	99 (35.5)	55 (82.1) [*]
CES-D scores, mean (SD)	7.0 (7.7)	6.5 (7.2)	8.9 (9.5) [†]
Use of depression medication, N (%)	34 (9.8)	26 (9.3)	8 (11.9)

^{*} p<.001,[†] p<.05,[§] p<.10[‡] cholesterol lowering medication

Table 2Significant Differences in *CES-D Scores* by Subgroup, mean (SD)

Subgroup	Not in subgroup	In subgroup
Economic hardship	6.2 (6.9)	10.1 (9.8) *
Unmarried	6.3 (7.1)	8.7 (8.9) †
Smoker	6.5 (7.3)	9.5 (9.7) †
Use of depression medication	6.5 (7.4)	11.6 (8.8) *

†
p<.05,*
p<.01

Table 3

Multivariate Predictors of CAC Progression.

	<i>Model 1: Baseline Predictors</i> N=346	<i>Model 2: Baseline Predictors + CAC at Baseline</i> N=346	<i>Model 3: Subset with CAC at Baseline</i> N=154
	RR (95% CI)	RR (95% CI)	RR (95% CI)
Black Race	0.68 (0.45,1.03)	0.66 (0.44,0.98) [*]	0.65 (0.43,0.99) [*]
Age [†]	1.32 (1.08,1.62) [‡]	1.12 (0.91,1.38)	1.10 (0.89,1.36)
BMI [†]	1.31 (1.11,1.54) [‡]	1.06 (0.90,1.25)	1.05 (0.88,1.25)
SBP [†]	1.28 (1.06,1.55) [*]	1.23 (1.06,1.44) [‡]	1.24 (1.06,1.46) [‡]
Use of statins [‡]	1.65 (0.96,2.83) [§]	1.45 (0.78,2.68)	1.38 (0.71,2.68)
Education ≤ High School	1.52 (1.02,2.27) [*]	1.47 (0.99,2.20) [§]	1.55 (1.03,2.33) [*]
Presence of CAC at Baseline		4.68 (2.43,9.01) ^{//}	
CES-D scores [†]	1.25 (1.06,1.47) [‡]	1.26 (1.10,1.44) ^{//}	1.31 (1.13,1.51) ^{//}

[†] standardized[§] p<.10,^{*} p<.05,[‡] p<.01,^{//} p<.001

Adjusted for time between scans, post-menopausal status and HT use (all non-significant at p=0.10).

[‡] cholesterol lowering medication