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Relation of Persistent Depressive Symptoms to Coronary Artery Calcification in Women Aged 46 to 59 Years

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Abstract

Depressive disorders have been associated with cardiovascular disease (CVD), but the impact of depression on early atherogenesis has not been well described, particularly in women and minorities. The relationship between repeated episodes of high depressive symptoms and coronary calcium (CAC) is unknown in women at midlife when depression is common. Participants in the Study of Women's Health Across the Nation Heart study were assessed annually for depressive symptoms (CES-D scale) over 5 years prior to CAC assessment and classified as high (CES-D ≥ 16) or not. CAC, measured by computed tomography, was analyzed as a categorical variable using cumulative logit partial proportional odds models. In these middle-aged women free of CVD and diabetes (194 black, 334 white), high depressive symptoms over five years were common; 19% had 1, 9% had 2, and 11% experienced ≥ 3 episodes. Coronary calcium was low; 54% had no CAC, 25% had scores between 0 and 10, and 21% had CAC ≥ 10 Agatston score. After adjusting for CVD risk factors, women with ≥ 3 episodes were twice as likely to have significant CAC (≥ 10 Agatston units) than women with no depressive episodes [OR (95% CI)=2.20 (1.13–4.28), p=0.020] with no difference by race. Women with 1 or 2 episodes did not differ from women with no episodes. In conclusion, in healthy women aged 46 to 59 years without clinical CVD or diabetes, persistent depressive symptoms were significantly associated with elevated CAC scores, suggesting that they are more likely to have pathophysiological and behavioral effects on the development of subclinical CVD than does a single episode of elevated depressive symptoms.

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Keywords

epidemiology; depressive symptoms; coronary artery calcification; midlife women

Introduction

Cardiovascular disease (CVD) in women increases substantially after age 45. Depression has been identified as a potential risk factor for CVD, and mid-life women are particularly vulnerable to depressive mood. Coronary calcium (CAC) correlates with atherosclerosis and predicts clinical events, but results from past studies of depression and CAC have been inconsistent. Major depressive disorders have been linked to higher levels of CAC cross-sectionally^{1, 2} and longitudinally,³ but depressive symptoms have been unrelated to CAC in cross-sectional studies.^{1, 4–7} In an older cohort⁸ a negative association was found between depressive symptoms and CAC level; women in the lowest quartile of depressive symptoms had the highest odds of CAC. In a younger cohort, high depressive symptoms, especially the subscale of depressive affect, were related to incident CAC.⁹ Whitehall II study¹⁰ participants with 2 episodes of high depressive symptoms at 3 times over a 10 year period) were more likely to have high levels of CAC, but the effect was observed only in men. Higher levels of depressive symptoms at SWAN Heart baseline were related to aortic but not coronary calcium in black women only,⁵ and to progression of CAC in both black and white women.¹¹ A history of recurrent major depression has also been related to CAC¹ and CAC progression³. However, recurrent depressive symptoms have not been investigated in relation to CAC level in a middle-aged biracial cohort of women. Therefore, we aimed to investigate whether persistently high levels of depressive symptoms are related to higher levels of CAC, whether this association varied by race, and whether this association was limited to certain subscales.

Methods

Baseline data were used from the SWAN Heart Study, an ancillary study of the Study of Women's Health Across the Nation (SWAN). The aim of the parent SWAN study is to examine the natural history of the menopausal transition in 3302 women from 5 ethnic backgrounds, recruited from 7 geographic sites in the United States.¹² The SWAN Heart Study was conducted at the Chicago and Pittsburgh sites only which, by design, recruited non-Hispanic white and black participants. The institutional review boards at each site approved all protocols; all women provided written informed consent.

SWAN Heart began in 2001–2003, coincident with the year 4 through 7 annual SWAN exams. A total of 608 participants were recruited (37% black). The analytic sample for the current study included 528 (87%) of the 608 SWAN Heart participants. The 80 exclusions were for clinical CVD (history of myocardial infarction, angina, intermittent claudication, cerebral ischemia, or revascularization, N=11), for diabetes (N=20), and for missing CAC scan (N=49). There were no differences in the variables presented in Table 1 between those who were and were not in the analytic sample.

CAC was measured by electron beam computed tomography (EBCT) in 2 passes. The first provided landmarks and the second provided the 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. ECG triggering was used so that each 100-millisecond exposure was obtained during the same phase of the cardiac cycle (60% of the RR interval). Calcification, using the method established by Agatston,¹³ was 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 arteries categorized as 0 (none), 1–10 (minimal), or >10 (moderate).¹⁴

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 1 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, 2 minutes apart, and averaged. Total cholesterol and high-density lipoprotein cholesterol (HDL-C) were analyzed on EDTA-treated plasma using standard methods.^{15, 16} Low density lipoprotein (LDL-C) was calculated using the Friedewald equation.¹⁷

Depressive symptoms were assessed using the Center for Epidemiological Studies Depression Scale (CES-D).¹⁸ 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. A score of 16 is typically used to identify potential clinical depression. This instrument has been validated with good test-retest reliability in racially diverse samples and has been utilized widely in epidemiological studies. Over the course of 5 study visits prior to the assessment of CAC, a visit where a participant exhibited high depressive symptoms (CES-D 16) was classified as a depressive episode. The number of depressive episodes was summed over the 5 visits and the covariate of interest defined as a 4 level categorical variable: 0, 1, 2, or 3 episodes. Self-reported anti-depressant medication used was verified by a clinical psychiatrist. Subscales of the CES-D were defined as in other published studies on subscales of the CES-D and CAC;^{9, 19} depressed affect (eg, sadness and loneliness), somatic symptoms (eg, poor appetite and sleep disturbance), interpersonal distress (eg, feeling disliked), and (lack of) positive affect (eg, happiness and life satisfaction). As there are no accepted cut-points for the subscales, the average score over 5 years up to CAC assessment was calculated to yield a measure of chronicity of these symptoms.

Participant characteristics were summarized using mean and standard deviation (SD) for continuous measures and N (%) for categorical measures. In order to detect overall trends across the 3 CAC categories, the Cochran-Armitage trend test was utilized for dichotomous characteristics and the Cochran-Mantel-Haenszel test was used for categorical

characteristics with >2 groups. For continuous characteristics, overall differences between the 3 CAC categories were examined with the ANOVA F-test, with contrasts employed to detect trends. For all characteristics, 3 pairwise comparisons were conducted, comparing the middle CAC category to the lowest, the highest to the middle, and the highest to the lowest. These were performed using the ANOVA contrast or the chi-square test, depending on the nature of the characteristic. All pairwise comparisons were adjusted using the Bonferroni correction, with $p < 0.017$ indicating a statistically significant result.

CAC is known to follow a highly right skewed distribution with many 0s in healthy populations.^{4, 5, 20} In the current study, 54% had a score of 0 Agatston units. Consequently, the relationship between CAC and covariates was assessed via a trichotomous dependent variable (0, >0 but <10, and ≥ 10 Agatston units) using cumulative logit models.²¹ Because the proportional odds assumption was not satisfied, partial proportional odds models were employed, allowing the effect of the covariates on the log odds of being in the upper 2 outcome categories to be different from the log odds of being in the highest outcome category. A backward stepwise procedure was utilized to determine which covariates had a significantly different effect on the pair of log odds. Continuous covariates were standardized to facilitate model interpretation. Models were rerun with each of the four component scores separately.

About 13% of participants had one or more visits with missing depressive symptoms. However, 96% of the sample had complete data on depressive symptoms for 4 years. Sensitivity analyses used multiple imputation. All statistical analyses were performed with SAS 9.2 (SAS version 9.2, SAS Institute, Inc, Cary, NC, USA) and STATA 12 (StataCorp. 2011. *Stata Statistical Software: Release 12*. College Station, TX: StataCorp LP). P-values <0.05 were considered statistically significant. The authors had full access to the data and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Table 1 shows the cohort characteristics overall and grouped by CAC level. On average, women were healthy but heavy (mean BMI=29) with blood pressure and lipids in the normal range. Economic hardship, marital status, smoking, hormone therapy, family history of CVD, cholesterol lowering medication use, and use of anti-depressant medication were not associated with CAC levels. There was a significant upward trend in the proportion of black women across the categories, mostly due to the substantial difference between the upper 2 categories relative to the 0 Agatston units category ($p = 0.013$, $p = 0.014$). There was an upward trend in the proportion of post-menopausal women across the CAC categories driven by a significant difference between the middle and highest CAC category ($p = 0.014$). The rate of blood pressure medication utilization increased across the categories, most notably between the upper 2 relative to the 0 Agatston units category (both $p < 0.001$). Participant age, BMI, SBP, DBP, LDL cholesterol, total cholesterol, and triglycerides all exhibited a positive trend across the CAC categories. The number of depressive episodes was marginally related to higher CAC levels in this overall test.

Table 2 shows characteristics of the cohort by the number of depressive episodes. Economic hardship, being unmarried, smoking, and use of anti-depressant medication were all positively associated, and HDL cholesterol was negatively associated with frequency of depressive episodes. No other covariates were significantly related to the frequency of depressive episodes.

Table 3 shows the results of the unadjusted as well as the adjusted cumulative partial proportional odds model relating the frequency of depressive episodes to CAC levels. Each point estimate can be interpreted as the multiplicative increase in the odds of response in either of the 2 highest categories or the highest category. Estimates for 1, 2, and 3 depressive episodes were similar in both the unadjusted and adjusted model. A woman with 3 depressive episodes had >2 times higher odds of being in the upper 2 CAC categories relative to a participant with 0 depressive episodes. Participants experiencing 1 or 2 depressive episodes did not exhibit higher odds of possessing higher levels of CAC relative to participants with no depressive episodes. Figure 1 displays the predicted CAC category membership by number of depressive episodes based on the adjusted model.

In the adjusted model, age, BMI, SBP, and cholesterol lowering medication use were significantly related to higher levels of CAC. For a given covariate, the violation of the proportional odds assumption was indicated by the presence of 2 unique point estimates, separately describing the effect of the covariate on the odds of response in either of the 2 highest categories and the highest category. A 1 SD higher SBP increased the pair of odds by 27%. Cholesterol lowering medication use was negatively associated with CAC levels.

Table 4 shows that, averaged over 5 years, the depressive symptoms subscales are similar to values in previous studies in older¹⁹ as well as in younger people.⁹ Only the subscales of depressed affect and interpersonal stress were significantly related to higher levels of CAC.

Discussion

We found that persistent depressive symptoms relate to CAC but that a single occurrence does not, suggesting that it is the persistence over time that is important. One previous study¹⁰ examined the relationship and did not observe an association in women. Compared to the British sample, our study population was larger (528 vs. 207) with a younger age range (47 to 57 vs. 53 to 76), and persistent depressive symptoms were more common (11% vs. 7%), as one would expect in women during the menopausal transition. The estimate of relative risk of higher CAC in our analysis was similar to that of the British study, although we used the lower Agatston score of 10 (instead of 100), a cutoff previously used to assess significant CAC²⁰ in healthy asymptomatic populations. Lastly, our method of analysis, i.e. cumulative partial proportional odds models, is more powerful than multivariate logistic regression. Another previous study⁹ found that depressive symptoms, measured at an average age of 40, predicted CAC incidence 5 years later. A similar effect was observed for the depressive affect but for no other subscale. In the current analysis, the subscales of depressive affect as well as interpersonal distress were significantly associated with CAC.

Participant age had a significantly different effect on the 2 log odds of being in the highest or 2 higher categories. Holding everything else constant, a 1 SD higher age increased the probability of being in the upper 2 CAC categories relative to the 0 category by 26%. The same difference in age resulted in a 65% higher probability of possessing ≥ 10 relative to <10 Agatston units. This non-homogeneity of the odds suggested that age, as a covariate, may differentiate better between higher levels of CAC (≥ 10 versus <10 Agatston units) than between CAC presence and absence (0 versus >0 Agatston units). This phenomenon was consistent with the finding (Table 1) that age did not differ in the lower 2 CAC categories but was significantly higher in the ≥ 10 Agatston units category. BMI on the other hand, appeared to better differentiate between presence and absence of CAC (0 versus >0 Agatston units) than between higher levels of CAC (≥ 10 versus <10 Agatston units). A possible explanation for the substantially different odds ratios of the association between BMI and CAC levels could be that a higher BMI level has an amplifying effect on the initial development of CAC but a smaller effect on its progression from lower to higher levels. Indeed, as can be seen in Table 1, the mean levels of BMI exhibit the largest difference between the lowest and the middle CAC category.

Limitations of our 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 annually, recalled over 1 week. We studied black and white women from large urban communities. Therefore, our results may not apply to women of other ethnic origins or from more rural areas.

Strengths of our study include the large well-characterized cohort of healthy black and white women free of clinical CVD of similar socio-economic background. CAC, depressive symptoms, and covariates were assessed in standard ways. Sensitivity analyses examining the impact of missing values of depressive episodes on the relationship of interest, as well as the removal of subjects with any missing values of depressive episodes from the analysis, did not have a noteworthy impact on the parameter estimates of interest nor their significance level.

In conclusion, in this large biracial cohort, persistently high depressive symptoms were significantly associated with higher levels of CAC. This effect remained significant even after controlling for age, BMI, and SBP, which were all very strongly associated with higher levels of CAC, suggesting that depressive symptoms are likely to have pathophysiological and behavioral effects on the development of subclinical CVD independent of standard CVD risk factors.

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Figure 1.
Coronary Artery Calcium by Number of Years with High Depressive Symptoms (CES-D=16+) over 5 Years

Table 1

Characteristics of the cohort overall and by CAC level.

Variable	CAC (A gatston units)			P-value ^a
	Total	0	> 0, < 10	10
	(n=528)	(n=285)	(n=134)	(n=109)
Age (years, mean [SD])	50.9 (2.9)	50.5 (2.8)	50.7 (2.9)	52.1 (2.6) [‡]
Black	194 (36.7%)	88 (30.9%)	58 (43.3%) [*]	48 (44.0%) [*]
Economic hardship	162 (30.7%)	86 (30.2%)	46 (34.3%)	30 (27.5%)
Unmarried	154 (29.2%)	85 (29.8%)	35 (26.1%)	34 (31.2%)
Education				
High School	91 (17.2%)	44 (15.4%)	25 (18.7%)	22 (20.2%)
Some College	154 (29.2%)	77 (27.0%)	42 (31.3%)	35 (32.1%)
College Degree	282 (53.6%)	164 (57.5%)	67 (50.0%)	52 (47.7%)
Smoker	89 (16.9%)	55 (19.3%)	16 (11.9%)	18 (16.5%)
Post-menopausal	143 (27.1%)	73 (25.6%)	30 (22.4%)	40 (36.7%) [‡]
Hormone Therapy use	25 (4.7%)	12 (4.2%)	7 (5.2%)	6 (5.5%)
Family history of CVD	352 (66.7%)	179 (62.8%)	100 (74.6%)	73 (67.0%)
Use of blood pressure medication	79 (15.0%)	22 (7.7%)	30 (22.4%) [*]	27 (24.8%) [*]
Statin use	23 (4.4%)	14 (4.9%)	6 (4.5%)	3 (2.8%)
Use of anti-depressant medication	52 (9.9%)	26 (9.1%)	12 (9.0%)	14 (12.8%)
BMI (kg/m ² , mean [SD])	29.0 (6.1)	25.8 (3.8)	31.6 (4.9) [*]	33.9 (7.5) [‡]
SBP (mmHg, mean [SD])	119.0 (15.6)	114.9 (14.3)	122.1 (14.6) [*]	125.7 (18.4) [*]
DBP (mmHg, mean [SD])	75.8 (9.9)	73.6 (9.4)	78.1 (9.5) [*]	78.9 (10.3) [*]
HDL cholesterol (mg/dL, mean [SD])	57.9 (14.5)	60.8 (14.8)	55.2 (13.5) [*]	53.8 (13.6) [*]
LDL cholesterol (mg/dL, mean [SD])	118.1 (31.3)	113.8 (29.3)	120.9 (33.5)	125.8 (32.0) [*]
Total cholesterol (mg/dL, mean [SD])	199.3 (36.4)	195.2 (33.6)	200.6 (38.5)	208.6 (39.0) [*]

CAC (Agatston units)				
	Total	0	> 0, < 10	10
Triglycerides (mg/dL, mean [SD])	114.7 (64.8)	102.2 (51.0)	120.5 (63.4) *	140.5 (86.8) *
				P-value ^a
Depressive Episodes				<.001
0	322 (61.0%)	178 (62.5%)	83 (61.9%)	61 (56.0%)
1	102 (19.3%)	53 (18.6%)	29 (21.6%)	20 (18.3%)
2	47 (8.9%)	29 (10.1%)	10 (7.5%)	8 (7.3%)
3	57 (10.8%)	25 (8.8%)	12 (9.0%)	20 (18.4%)

^aThe Cochran-Armitage trend test was used for dichotomous characteristics, the Cochran-Mantel-Haenszel test was used for categorical characteristics with more than 2 categories (i.e. education), and an ANOVA F-test was used for continuous characteristics.

* p< 0.05 compared with 0 Agatston units adjusted per Bonferroni

[†] p< 0.05 compared with > 0, < 10 Agatston units adjusted per Bonferroni

[^] Cholesterol lowering medication

Table 2

Characteristics of the cohort by number of depressive episodes.

Variable	Depressive Episodes				
	0 (n=322)	1 (n=102)	2 (n=47)	3 or more (n=57)	p-value ^a
Age (years, mean [SD])	50.9 (3.0)	50.8 (2.6)	50.7 (2.6)	51.0 (2.9)	
Black	114 (35.4%)	35 (34.3%)	20 (42.6%)	25 (43.9%)	
Economic hardship	72 (22.4%)	39 (38.2%)	23 (48.9%)	28 (49.1%)	***
Unmarried	87 (27.0%)	25 (24.5%)	17 (36.2%)	25 (43.9%)	**
Education					
High School	52 (16.2%)	19 (18.6%)	7 (14.9%)	13 (22.8%)	
Some College	83 (25.8%)	32 (31.4%)	19 (40.4%)	20 (35.1%)	
College Degree	187 (58.1%)	51 (50.0%)	21 (44.7%)	24 (42.1%)	
Smoker	48 (14.9%)	11 (10.9%)	9 (19.2%)	21 (36.8%)	***
Post-menopausal	88 (27.3%)	24 (23.5%)	12 (25.5%)	19 (33.3%)	
Hormone Therapy use	12 (3.7%)	3 (2.9%)	6 (12.8%)	4 (7.0%)	
Family history of CVD	219 (68.0%)	71 (69.6%)	26 (55.3%)	36 (63.2%)	
Use of blood pressure medication	48 (14.9%)	12 (11.8%)	8 (17.0%)	11 (19.3%)	
Statin use	14 (4.35%)	4 (3.9%)	4 (8.5%)	1 (1.8%)	
Use of anti-depressant medication	13 (4.0%)	13 (12.8%)	12 (25.5%)	14 (24.6%)	***
BMI (kg/m ² , mean [SD])	28.9 (6.2)	29.5 (5.8)	28.4 (5.4)	29.0 (6.8)	
SBP (mmHg, mean [SD])	119.3 (15.4)	118.7 (15.7)	116.9 (18.3)	119.2 (17.8)	
DBP (mmHg, mean [SD])	75.9 (9.9)	76.3 (9.8)	74.0 (9.9)	76.0 (10.2)	
HDL cholesterol (mg/dL, mean [SD])	59.3 (15.0)	56.7 (13.1)	55.6 (13.2)	54.5 (14.6)	*
LDL cholesterol (mg/dL, mean [SD])	117.2 (30.3)	116.9 (31.7)	126.3 (33.4)	118.4 (33.9)	
Total cholesterol (mg/dL, mean [SD])	199.3 (36.5)	196.6 (32.9)	204.8 (38.5)	199.5 (40.0)	
Triglycerides (mg/dL, mean [SD])	112.8 (65.3)	113.6 (60.5)	111.5 (49.5)	130.2 (78.4)	

^aThe Cochran-Armitage trend test was used for dichotomous characteristics, the Cochran-Mantel-Haenszel test was used for categorical characteristics with more than two categories (i.e. education), and an ANOVA linear trend test was used for continuous characteristics.

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Cholesterol lowering medication

p<0.001
**
p<0.01
*
p<0.05

Table 3

Cumulative logit partial proportional odds model for number of depressive episodes and coronary calcium level; unadjusted and adjusted for cardiovascular disease risk factors.

	Minimally Adjusted Model	Fully Adjusted Model
Parameter	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Intercept (CAC units: 0, >0)	0.862 (0.646–1.151)	0.884 (0.620–1.859)
Intercept (CAC units: 10, >10)	0.167 (0.119–0.234)	0.165 (0.111–1.118) ***
Age (CAC units: 0, >0) ^a	1.287 (1.055–1.571) *	1.271 (1.006–2.736) **
Age (CAC units: 10, >10) ^a	1.673 (1.318–2.122) ***	1.662 (1.273–3.571) ***
African American	0.904 (0.612–1.336)	0.794 (0.525–1.691)
BMI (CAC units: 0, >0) ^a	5.625 (4.220–7.499) ***	5.373 (3.958–52.327) ***
BMI (CAC units: 10, >10) ^a	2.961 (2.319–3.781) ***	2.790 (2.154–8.622) ***
SBP ^a	--	1.267 (1.023–2.782) **
HDL ^a	--	0.901 (0.730–2.075)
Education		
High School	--	1.492 (0.888–2.431)
Some College	--	0.909 (0.584–1.793)
College Degree	--	Reference
Post-menopausal	--	1.099 (0.674–1.961)
Cholesterol lowering medication	--	0.309 (0.119–1.126) **
Depressive Episodes		
0	Reference	Reference
1	1.122 (0.686–1.836)	1.134 (0.685–1.985)
2	0.987 (0.489–1.992)	1.035 (0.506–1.659)
3 or more	2.277 (1.181–4.393) *	2.200 (1.130–3.095) **

^a standardized covariate

^b minimally adjusted: adjusted for age and BMI at CAC assessment

^c fully adjusted: adjusted for age, BMI, systolic blood pressure, high density cholesterol, post-menopausal status, and cholesterol lowering medication at CAC assessment

p-value <0.001,

**
p-value <0.01,

*
p-value <0.05

Table 4

Median (Interquartile Range) of Components of depressive symptoms [CES-D], averaged over 5 years up to and including the visit with coronary calcium assessment; Cumulative logit partial proportional odds model for depressive symptom clusters and coronary calcium level, adjusted for cardiovascular disease risk factors.

Parameter	N of items/year (score range)	Mean [SD]	Minimally Adjusted Model		Fully Adjusted Model	
			Odds Ratio (95% CI)		Odds Ratio (95% CI)	
Depressed Affect	7 (0 – 21)	7.47 (6.17)	1.101 (1.017–1.193) [*]		1.109 (1.021–1.204) [*]	
Somatic Symptoms	7 (0 – 21)	2.12 (2.32)	1.032 (0.962–1.106)		1.022 (0.951–1.098)	
Positive Affect (reverse coded)	4 (0 – 12)	10.56 (1.65)	1.061 (0.945–1.192)		1.067 (0.948–1.202)	
Interpersonal Distress	2 (0 – 6)	0.26 (0.51)	1.441 (1.001–2.075) [*]		1.462 (1.009–2.118) [*]	

^a minimally adjusted: adjusted for age and BMI at CAC assessment

^b fully adjusted: adjusted for age, BMI, systolic blood pressure, high density cholesterol, post-menopausal status, and cholesterol lowering medication at CAC assessment

^{*} p-value <0.05