Published in final edited form as:

J Affect Disord. 2020 November 01; 276: 267–271. doi:10.1016/j.jad.2020.07.042.

Association of Depressive Symptom Severity with Coronary Artery Calcium: The Dallas Heart Study

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Abstract

Background: Previous studies have yielded mixed results regarding the relationship between depressive symptoms and coronary artery calcium (CAC). This analysis sought to evaluate this relationship using a multiethnic, population-based cohort.

Methods: Data were extracted from the second phase of the Dallas Heart Study (DHS-2). Depressive symptom severity was measured with the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS), a validated depressive symptom severity scale. A regression analysis was performed using QIDS score as the predictor variable and CAC as the outcome variable. Covariates included age, sex, ethnicity, diabetes, hypertension, smoking, systolic blood pressure, total cholesterol, HDL cholesterol, and body mass index.

Results: The cohort consisted of 2,293 individuals with a mean age of 50 years and included 47.1% female and 47.1% black participants. The mean QIDS score was 4.37(±3.69), and 43.3% had CAC > 0. Regression results indicated that QIDS does not statistically significantly predict whether one does or does not have CAC, when controlling for age, sex, and ethnicity ($\beta = .088$, $p = 0.240$, OR = 1.092, 95% CI 0.943-1.264).

Limitations: Cross sectional design is limited to one point in time, very depressed patients with higher CAC burden may not have participated, and depressive symptoms may be associated with subclinical atherosclerosis differently with a formal diagnosis of depression.

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Author Contributions

Amber Khan and Jayme Palka contributed to the data analysis. Amber Khan contributed to writing the manuscript. Dr. Khera, Dr. Joshi, Jayme Palka and Dr. Brown edited the manuscript and provided expertise from the fields of cardiology, psychiatry and statistics.

Declaration of Competing Interest

Dr. Joshi receives grant support from AHA, Novo Nordisk, GlaxoSmithKline, and AstraZeneca, and serves as a consultant for Regeneron and Bayer. Dr. Brown has grants from NIH, the Stanley Medical Research Institute and Otsuka, and serves on an advisory board for Allergan.

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Conclusion: Depressive symptoms were not associated with presence or severity of CAC in a multiethnic population based sample. Future studies are needed to determine if other prognostic markers of coronary heart disease are associated with depressive symptoms.

Keywords

Depression; coronary artery calcium; QIDS

Introduction

Coronary artery disease is the leading cause of mortality in the United States. In addition, billions of dollars in healthcare expenses and lost productivity are attributable to the cost of living with coronary artery disease (Benjamin et al., 2018). Thus, there has been great interest in identifying and addressing modifiable risk factors for this condition. Depression is a modifiable risk factor that has been independently associated with coronary artery disease (Rozanski et al., 2011). However, the pathophysiology that links coronary heart disease and depression remains unclear (Carney and Freedland, 2016).

One hypothesis for a mechanism that mediates the effects of depression on coronary heart disease is that depression may be associated with increased subclinical atherosclerosis in the form of coronary artery calcium (CAC), a marker that can be assessed through noninvasive testing (Benjamin et al., 2018). In several studies, CAC score has been shown to be a strong predictor of coronary heart disease events independently of other risk factors (Erbel et al., 2010; Pletcher et al., 2013; Taylor et al., 2006). In addition, this prognostic nature of CAC has been reproduced in people of different ages and different racial and ethnic backgrounds (Carr et al., 2017; Detrano et al., 2008).

However, the data regarding the association of depressive symptoms with CAC have been mixed. Diez Roux et al. found that in a multiethnic population of 6,789 adults, there was no association between CAC and depressive symptoms (Diez Roux et al., 2006). Santos et al., in a cohort of 4,279 adults, observed a positive association between CAC and symptoms of depression and anxiety (Santos et al., 2016). A 2017 meta-analysis by Ali et al. found that among 24 studies of depression and CAC, 12 studies found a positive association, 10 studies found no association and 2 studies found a negative association between depression and CAC (Ali et al., 2017). The heterogeneity of results has been attributed to differences in study population, measurement of depression or depressive symptoms, and study design (Ali et al., 2017). Furthermore, CAC has been shown to significantly differ between racial groups (McClelland et al., 2006; Newman et al., 2002). In particular, CAC has been shown to be higher in white males than black males, and to be lowest in black and Hispanic females (Benjamin et al., 2018; McClelland et al., 2006). Such differences may have implications for sex and ethnicity specific differences in the association between depression and CAC.

We performed a cross-sectional analysis of 2,293 adults enrolled in the Dallas Heart Study (DHS), an epidemiological sample of individuals living in Dallas County with oversampling of African Americans. We evaluated the association between depressive symptom severity and CAC.

Methods

The Dallas Heart Study is a multiethnic population-based sample of the residents of Dallas County (Victor et al., 2004). The aim of Dallas Heart Study was to identify social and biological factors contributing to cardiovascular disease within this population. Data collection began on July 1, 2001 and was completed on December 31, 2002, known as phase one of the study (DHS-1). A second phase of the DHS (DHS-2) was conducted from September 1, 2007 to December 31, 2009 and consisted of self-reported data in a questionnaire, biomarker data and imaging data (Victor et al., 2004). The data in this study comes from participants of DHS-2. All participants provided written, informed consent prior to participation, and the study was approved the University of Texas Southwestern Institutional Review Board.

Depressive symptoms were assessed using the 16-item Quick Inventory of Depressive Symptomatology-Self Report (QIDS), a depressive symptom severity scale that is based on the nine criteria listed in the Diagnostic and Statistical Manual (DSM) IV for the diagnosis of major depressive disorder. The questions in the assessment evaluate depressive symptoms in the week prior to assessment and are scored according to frequency of symptoms. QIDS has been used in several prior studies that demonstrate its utility as a depression screen. A prior study demonstrates strong internal validity and strong correlation with 30-item self-report Inventory of Depressive Symptomatology and the 17-item clinician-rated Hamilton Rating Scale for Depression (Brown et al., 2008). Another prior study shows that the tool has strong validity and reproducibility as a depression screen in the clinical setting (Rush et al., 2003). Finally, a systematic review of studies using the QIDS shows that it has strong internal consistency (Reilly et al., 2015).

Multi-detector computed tomography (MDCT) on a single scanner (Toshiba Aquilion 64-slice MDCT) was used to measure CAC. A score using Agatston units quantified the severity of CAC (Paixao et al., 2017). Each individual was scanned twice, and the mean of the two scans were used to compute the final Agatston score. In the instance of only one available CT scan, that single result was used.

To be included in the study, participants must have both CAC and QIDS scores recorded. A total QIDS score was considered missing only if all 16 item scores were also missing; otherwise, a total QIDS score was calculated with the available item scores. Participants with a history of coronary artery disease ($n = 119$) were excluded from the study. Coronary artery disease history was determined by a self-reported history of myocardial infarction or angina. Based on these criteria, 3082 individuals were eligible for inclusion. Of these $n = 3082$ participants, a further 789 individuals were excluded from the analysis due to missing covariate data. Of the 789 excluded, 526 were missing a CAC score, 335 were missing a QIDS score, 59 were missing both total cholesterol or HDL cholesterol, 6 were missing systolic blood pressure, and 24 were missing BMI. Note that a single participant may have been missing data on more than one covariate. Participant characteristics were compared by level of QIDS score. Hypertension was determined by a systolic blood pressure >140 mmHg or self-reported history of hypertension. Diabetes history was determined by a history of

postprandial glucose >200 mg/dl, fasting glucose >126mg/dl. self-report or use of hypoglycemic medications.

A series of regression analyses was performed to determine the predictive ability of QIDS for CAC after adjusting for relevant covariates using IBM SPSS Statistics version 23.0 (Armonk, NY: IBM Corp.) All tests were evaluated at an $\alpha = .05$ with Bonferroni corrections for multiple comparisons. Past studies have shown a right skew in CAC (Newman et al., 2001). After confirming that CAC was right skewed in the present sample, we used the natural log of CAC in a portion of the analyses. As such, CAC was examined in three ways: (1) categorically scaled CAC in which CAC was dichotomized into $CAC = 0$ and $CAC > 0$, (2) continuously scaled CAC after applying a natural log transformation ($\ln(CAC+1)$) to correct for skewness, and (3) continuously scaled CAC after applying a natural log transformation for $\ln(CAC+1)$ only participants with $CAC > 0$. Thus analyses were performed on people with or without any CAC (dichotomous), all CAC values as a continuous outcome and as a continuous outcome only in those with some CAC ($CAC > 0$). Further, QIDS was examined in two ways: (1) continuous (models 1a – 6a) and (2) dichotomized (models 1b – 6b) based on depression severity threshold of 11, consistent with moderate depression (Brown et al., 2008). Additionally, other covariates showed skew, including body mass index (BMI), QIDS, systolic blood pressure, and HDL cholesterol and were also log transformed. Finally, categorical variables with more than two levels (i.e., ethnicity and smoking history) were dummy coded.

In model 1, dichotomous CAC (i.e., $CAC = 0$ and $CAC > 0$) was regressed on QIDS and demographic predictors (i.e., age, sex, and ethnicity) using logistic regression. In model 2, dichotomous CAC was regressed on QIDS, demographic predictors, and biometric and behavioral covariates (i.e., total cholesterol, HDL cholesterol, smoking, diabetes, systolic blood pressure, hypertension, and BMI), again using logistic regression. In model 3, $\ln(CAC + 1)$ was regressed on QIDS and demographic predictors (i.e., age, sex, and ethnicity). In model 4, $\ln(CAC + 1)$ was regressed on QIDS, demographic predictors, and biometric and behavioral covariates. In model 5, $\ln(CAC + 1)$ was regressed on QIDS and demographic predictors (i.e., age, sex, and ethnicity). Finally, in model 6, $\ln(CAC + 1)$ was regressed on QIDS, demographic predictors, and biometric and behavioral covariates (i.e., total cholesterol, HDL cholesterol, smoking, diabetes, systolic blood pressure, hypertension, and BMI). Finally, regression analyses using continuously scaled QIDS were repeated; these were identical to the adjusted models indicated above, but with the inclusion of $QIDS \times sex$ and $QIDS \times ethnicity$ interaction terms. For models 1 – 6, QIDS was continuously scaled. For models 3 – 6 multiple linear regression was used and for models 5 and 6 only participants with $\ln(CAC + 1) > 0$ were included. For simplicity, each outcome is referred to simply as “CAC.”

Results

The study sample of 2,293 individuals had a mean age of 50 (± 10.6) years and was evenly distributed by sex. Nearly half of the sample was non-Hispanic Black, 48.3 % had a history of hypertension and 43% considered themselves to be current or former smokers. The median BMI was 29.41 kg/m² (IQR = 8.3) and the median total cholesterol was 191 mg/dL

(IQR = 50). The median QIDS score was 3 (IQR = 4) and median CAC score was 0 (IQR = 17.0).

Table 1 displays the characteristics by QIDS score. Statistically significant differences between low QIDS and high QIDS were found for ethnicity ($\chi^2 = 15.12$, $p = .002$), sex ($\chi^2 = 27.76$, $p < .001$), and smoking status ($\chi^2 = 20.47$, $p < .001$). Among those with CAC > 0, the median CAC score in the low QIDS group was 33.93 while the median CAC score in the high QIDS group was 17.98. The proportion of individuals with CAC > 0 was similar between those with high vs. low QIDS (43.5% vs. 40.2%, $\chi^2 (1) = .694$, $p = .405$; Figure 1)

We performed 18 regression analyses to determine the association between QIDS scores and CAC when controlling for covariates (Tables 2 and 3). Results from model 1a indicate that QIDS does not statistically significantly predict whether one does or does not have CAC, when controlling for only age, sex, and ethnicity (Table 2, $\beta = .088$, $p = 0.240$, OR = 1.092, 95% CI for OR: 0.943-1.264). However, age and sex were statistically significant predictors of CAC. QIDS remained statistically non-significant when controlling for biometric and behavioral covariates in model 2a (Table 2, $\beta = -0.002$, $p = 0.980$, OR = 0.998, 95% CI for OR: 0.854-1.166). Results from model 3a and 4a again suggest that QIDS is not a statistically significant predictor of CAC when controlling for demographic covariates (Table 2, $b = 0.042$, $p = 0.503$, 95% CI for b : -0.080-0.164) or when controlling additionally for biometric and behavioral covariates (Table 2, $b = -0.034$, $p = 0.582$, 95% CI for b : -0.154-0.086). Results from models 5a and 6a indicate that QIDS does not statistically significantly predict CAC when controlling for demographic covariates (Table 2, $b = -8.406$, $p = 0.783$, 95% CI for b : -68.144-51.332) or additional biometric and behavioral covariates (Table 2, $b = -0.042$, $p = 0.655$, 95% CI for b : -0.255-0.141). QIDS was dichotomized to <11 and >11 based on the threshold for clinically significant depressive symptoms, and we found that when controlling for covariates in logistic regression using the same parameters as in Table 2 for CAC, there was no statistically significant association between CAC and QIDS even when QIDS was dichotomized based on depression severity (Table 3). Finally, all interaction terms across the six models were found to be statistically non-significant. In the interest of space, results are not reported in tabular form. Therefore, the QIDS score was not associated with the presence or severity of CAC.

Discussion

In a multiethnic epidemiological sample of 2,293 adults, we found that there was no statistically significant association between depressive symptoms and CAC. Our findings are consistent with past studies that also found no association between depressive symptoms and CAC (Devantier et al., 2013; Diez Roux et al., 2006; Rozanski et al., 2011) but diverge from those studies that have found a positive association between depressive symptoms and CAC in cross-sectional analysis (Bellettiere et al., 2016; Santos et al., 2016). Both positive studies used different scales to assess depressive symptoms, which may be related to the difference in findings. Further, our population sample was ethnically and racially diverse in comparison to several positive studies in which the population was predominantly white. Our negative finding is consistent with the one other major study in the field also using a multiethnic

population, despite the differences in clinical scales used to assess depressive symptoms (Diez Roux et al., 2006).

Additionally, the burden of calcified plaque may not represent the pathway through which depression affects clinical heart disease. CAC does not account for non-calcified plaque nor does it necessarily represent other markers for CVD events. There may be a marker other than CAC in the progression of atherosclerosis that is more predictive of disease and may be impacted by depressive symptoms.

Depression has a well-known association with coronary heart disease, yet the mechanism that underlies this is unclear and merits further research (Carney and Freedland, 2016). The findings in this study warrant further research into other mechanisms that may be shared between coronary artery disease and depression. One alternative mechanism through which depression may be linked to atherosclerotic disease is inflammation. Inflammation in the atherosclerotic process promotes endothelial dysfunction and plaque instability leading to increased risk of formation and rupture of atherosclerotic plaques (Ross, 1999). However, elevated inflammatory markers have also been observed in people with depressive symptoms and depression (Howren et al., 2009; Valkanova et al., 2013; Wium-Andersen et al., 2013), and inflammation in both processes may have synergistic effects. Although, in the DHS sample, the inflammatory biomarker high sensitivity C-reactive protein was not significantly related to QIDS-SR scores (Huckvale, 2020). Alternatively, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis as measured by elevations in the stress hormone, cortisol, may mediate the association between depression and increased atherosclerosis (Zunszain et al., 2011). Plasma and urine cortisol levels have been shown to be elevated in individuals with CAD, and a smaller decline in diurnal cortisol has been associated with elevated coronary artery calcium (Matthews et al., 2006; Nijm and Jonasson, 2009). Further research is needed due to the heterogeneity of findings regarding the association of hormonal and inflammatory markers with depression, which are markers of processes that may be shared between depression and atherosclerosis.

Limitations of the study include the cross-sectional nature of analysis. Depressive symptoms and CAC assessed at one point in time may not be representative of changes over time. In addition, very depressed patients who may have also had higher CAC burden may not have participated in the study. Studies that have shown a positive association between depressive symptoms and CAC were prospective and specifically showed an association between depressive symptoms or depression and increased prevalence of elevated CAC in later years (Janssen et al., 2016; Stewart et al., 2012). Approximately 17% of the participants were missing CAC data and as such, were excluded from our study. While we chose to refrain from imputing missing values for our outcome variable of interest, other researchers may choose to examine any deviations from our results after implementing imputation. In addition, the diagnosis of depression is based on the DSM criteria, which were not used in the assessment of depression though the scale used is derived from the DSM. The association between clinical depression, as diagnosed using the DSM criteria in a clinical interview, and subclinical atherosclerosis may differ from that of depressive symptoms and subclinical atherosclerosis (Tiemeier et al., 2004). However, the scale used in this study, QIDS-SR₁₆, is derived directly from the nine DSM criteria for major depressive disorder.

Strengths of the study include the size of the sample studied and diversity of the participants. To our knowledge, only one other study in this field evaluates the relationship between CAC and depression in a large, multiethnic population, and there is a need for studies in diverse populations. Our study differs from the previous large multiethnic population-based study by the use of the particular validated instrument to assess depressive symptoms. The QIDS-SR₁₆ scale is unique amongst depression assessment tools because this scale has been shown to better assess changes in depressive symptoms in response to treatment and to correlate more closely to the DSM criteria for a diagnosis of depression than other scales (Weiss et al., 2015). In addition, the population in the current report is younger than those in the prior large study with a broader age spectrum and lower mean age of participants (Diez Roux et al., 2006). This study also consists of a younger population than several other population based studies in this field (Diez Roux et al., 2006; Hernandez et al., 2014; O'Malley et al., 2000). This is significant because in several studies in which positive associations were found, the finding was strongest in older adults (Santos et al., 2016). It is well known that coronary artery calcification increases with age, and there is a need for more studies in younger populations.

In conclusion, this cross sectional-analysis of a multiethnic population does not support an association between depressive symptoms and CAC. Future longitudinal studies are needed in multiethnic populations to determine if there is an association between depressive symptoms and CAC over time. In addition, future research should be directed towards other markers of subclinical atherosclerosis that may demonstrate a stronger association with depression.

Acknowledgments

Role of funding source

Supported in part by grant UL1TR001105 from the National Center for Advancing Translational Sciences, National Institutes of Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Highlights

- No association was found between QIDS score and presence of coronary artery calcium
- No association was found between QIDS score and severity of coronary artery calcium
- Results were in a sample younger and more racially diverse than in prior studies

Figure 1.
Prevalence of CAC in Individuals with Low vs. High QIDS Score

Table 1

Descriptive Statistics for Included Participants

Categorical Variables	Whole Sample		QIDS < 11		QIDS 11	
	N	%	N	%	N	%
Sex						
Female	1356	47.1	1230	57.9	126	75.4
Male	937	40.9	896	42.1	41	24.6
Ethnicity						
Non-Hispanic Black	1080	47.1	988	46.5	92	55.1
Non-Hispanic White	820	35.8	784	36.9	36	21.6
Hispanic	338	14.7	304	14.3	34	20.4
Other	55	2.4	50	2.4	5	3.0
Diabetic	334	14.6	306	14.4	28	16.8
Hypertensive	1107	48.3	1024	48.2	83	49.7
Former Smoker	522	22.8	497	23.4	25	15.0
Current Smoker	486	21.2	431	20.3	55	32.9
Never Smoked	1285	56.0	1198	56.3	87	52.1
CAC dichotomous						
CAC = 0	1301	56.7	1202	52.44	99	4.3
CAC > 0	992	43.3	924	40.3	68	3.0
Continuous Variables	Mean	SD	Mean	SD	Mean	SD
Age	50.0	10.6	50.1	10.7	49.1	8.9
QIDS	4.4	3.7	3.6	2.3	14.2	3.6
Total Cholesterol	193.7	38.5	193.7	38.6	192.8	38.3
HDL	52.9	15.1	52.9	15.1	53.1	14.9
SBP	131.4	19.0	131.3	18.9	132.9	19.7
BMI	30.4	6.5	30.3	6.4	30.8	6.7
CAC	91.1	382.1	94.3	393.0	51.1	193.1

Note. Valid N = 2293.

Table 2

Results for CAC(dependent variable) regressed on continuous QIDS

Model	Outcome Variable	Analytic <i>n</i>	b	β	<i>p</i>	OR	95% CI	
							Lower	Upper
1a	Dichotomized CAC [†]	2319	-	0.088	.240	1.092	0.943	1.264
2a	Dichotomized CAC [†]	2293	-	-0.002	.980	0.998	0.854	1.164
3a	CAC ^{††}	2319	0.042	0.062	.503	-	-0.080	0.164
4a	CAC ^{††}	2293	-0.034	-0.010	.582	-	-0.154	0.086
5a	CAC > 0 ^{†††}	1004	-8.406	-0.009	.783	-	-68.144	51.332
6a	CAC > 0 ^{†††}	992	-0.042	-0.012	.655	-	-0.225	0.141

Note. 95% CI = 95% confidence interval.

[†] Dichotomized CAC is dichotomized between CAC = 0 and CAC > 0.

^{††} CAC includes ln(CAC+1) as the outcome for all continuous values including 0.

^{†††} CAC > 0 includes CAC as a continuous variable only among those with prevalent CAC (CAC > 0). In all models, QIDS is treated as a continuous predictor variable. Models 1a, 3a, and 5a are basic models adjusted for age, sex and ethnicity. Models 2a, 4a, and 6a are adjusted for age, sex and ethnicity, as well as diabetes, hypertension, smoking, total cholesterol, HDL, systolic blood pressure, and BMI. Odds ratios (OR) are presented in an unstandardized metric.

Table 3

Results for CAC (dependent variable) regressed on dichotomized QIDS (QIDS < 11; QIDS ≥ 11)

Model	Outcome Variable	Analytic <i>n</i>	<i>b</i>	β	<i>p</i>	OR	95% CI	
							Lower	Upper
1b	Dichotomized CAC [†]	2319	-	0.114	.523	1.120	0.791	1.588
2b	Dichotomized CAC [†]	2293	-	0.073	.698	1.076	0.744	1.556
3b	CAC ^{††}	2319	-0.036	-0.004	.811	-	-0.332	0.260
4b	CAC ^{††}	2293	-0.083	-0.010	.572	-	-0.373	0.206
5b	CAC > 0 ^{†††}	1004	-68.613	-0.018	.497	-	-0.592	0.287
6b	CAC > 0 ^{†††}	992	-0.152	-0.029	.353	-	-213.442	76.216

Note. 95% CI = 95% confidence interval.

[†]Dichotomized CAC is dichotomized between CAC = 0 and CAC > 0.

^{††}CAC includes ln(CAC+1) as the outcome for all continuous values including 0.

^{†††}CAC > 0 includes CAC as a continuous variable only among those with prevalent CAC (CAC > 0). In all models, QIDS is treated as a dichotomized variable (QIDS < 11; QIDS ≥ 11). Models 1b, 3b, and 5b are basic models adjusted for age, sex and ethnicity. Models 2b, 4b, and 6b are adjusted for age and sex, as well as ethnicity, diabetes, hypertension, smoking, total cholesterol, HDL, systolic blood pressure, and BMI. Odds ratios are presented in an unstandardized metric. Odds ratios (OR) are presented in an unstandardized metric.