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## Association of the interaction between smoking and depressive symptom clusters with coronary artery calcification: The CARDIA study

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### Abstract

**Objective**—Depressive symptom clusters are differentially associated with prognosis among patients with cardiovascular disease (CVD). Few studies have prospectively evaluated the association between somatic symptoms and risk for CVD. Previously, we observed that smoking and total depressive symptoms were synergistically associated with coronary artery calcification (CAC). The purpose of this study was to determine whether the smoking by depressive symptoms interaction, measured cumulatively over 25 years, differed by depressive symptom cluster (negative affect, anhedonia, and somatic symptoms) in association with CAC.

**Methods**—Participants (N=3,189: 54.5% female; 51.5% Black; average age=50.1 years) were followed from 1985–1986 through 2010–2011 in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Smoking exposure was measured by cumulative cigarette packyears (cigarette packs smoked per day × number of years smoking; Year 0 through Year 25). Depressive symptoms were measured using a 14-item, 3-factor (negative affect, anhedonia, somatic symptoms) analysis of the Center for Epidemiologic Studies Depression (CES-D) Scale (Years 5, 10, 15, 20, and 25). CAC was assessed at Year 25. Logistic regression models were used to evaluate the association between the smoking by depressive symptom clusters interactions with CAC (=0 vs. >0), adjusted for CVD-related sociodemographic, behavioral, and clinical covariates.

**Results**—907 participants (28% of the sample) had CAC >0 at Year 25. The depressive symptom clusters did not differ significantly between the two groups. Only the cumulative somatic symptom

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cluster by cumulative smoking exposure interaction was significantly associated with CAC >0 at Year 25 ( $p=.028$ ). Specifically, adults with elevated somatic symptoms (score 9 out of 18) who had 10, 20, or 30 packyears of smoking exposure had respective odds ratios (95% confidence intervals) of 2.06 (1.08–3.93), 3.71 (1.81–7.57), and 6.68 (2.87–15.53),  $ps<.05$ . Negative affect and anhedonia did not significantly interact with smoking exposure associated with CAC >0,  $ps>.05$ .

**Conclusions**—Somatic symptoms appear to be a particularly relevant cluster of depressive symptomatology in the relationship between smoking and CVD risk.

### Keywords

depression; depressive symptom clusters; somatic symptoms; smoking; coronary artery calcification (CAC); cardiovascular disease risk; prospective study

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In 2014, the American Heart Association elevated depression to the level of risk factor for recurrent cardiovascular disease (CVD) (Lichtman et al., 2014). Mounting evidence indicates that depression may be a risk factor for incident CVD (Nicholson, Kuper, & Hemingway, 2006; O’Neil, Fisher, Kibbey, Jacka, Kotowicz, Williams, Stuart, Berk, Lewandowski, Taylor, et al., 2016). Recently, researchers demonstrated that adding baseline depression to the Framingham Risk Score produced modest but significant improvements in the prediction of cardiac events among women over 18 years of follow-up (O’Neil, Fisher, Kibbey, Jacka, Kotowicz, Williams, Stuart, Berk, Lewandowski, Atherton, et al., 2016).

Because of the extended length of time required for adults to develop clinical CVD events and the desire to identify precursors to clinical disease, researchers frequently measure coronary artery calcification (CAC), a measure of subclinical atherosclerosis in the coronary arteries (Greenland et al., 2007; Pletcher, Tice, Pignone, & Browner, 2004), which is a strong and independent imaging biomarker of risk in men and women across various races and ethnicities (Detrano et al., 2008). Several studies have reported significant relationships between depressive symptomatology and CAC (e.g., Hamer, Kivimaki, Lahiri, Marmot, & Steptoe, 2010). Furthermore, in a recent study, we observed that smoking and depressive symptoms had a synergistic association with subclinical atherosclerosis, where higher lifetime smoking exposure and depressive symptoms were synergistically associated with higher odds of CAC (Carroll et al., In Press).

Depression is multi-faceted and can vary greatly in the course, severity, and symptomatology, and these facets of depression have been shown to have differential associations with recurrent cardiac events or CVD mortality. Depending on the study, depressive symptom clusters may include negative affect (i.e., depressed or sad mood), anhedonia (i.e., lack of interest, pleasure, or positive affect), somatic symptoms (e.g., sleep disturbance, changes in appetite), cognitive issues (e.g., difficulty concentrating), and interpersonal disturbance (e.g., loneliness, shame around others). Among patients with prevalent CVD, studies comparing dimensions of depression for predicting cardiac outcomes consistently find that somatic symptoms are consistently and strongly related to cardiac outcomes (Baune et al., 2012; Carney & Freedland, 2012).

Understanding how different depressive symptom clusters are associated with CAC may provide a better understanding of the mechanisms by which depressive symptoms may increase risk for CVD. There is some evidence that somatic symptoms are associated with incident CVD (Hawkins, Callahan, Stump, & Stewart, 2014). On the other hand, Stewart et al. (2012) found that the negative affect cluster (but not the anhedonia, somatic symptoms, or interpersonal disturbance clusters) predicted 5-year incidence of CAC. To our knowledge, no studies examining CAC have evaluated the interaction between depressive symptom clusters and smoking.

The purpose of this study was to evaluate if and how different clusters of depressive symptoms would interact with smoking exposure in relation to CAC, indicating the development of preclinical coronary artery disease. Using methodology consistent with our recent study (Carroll et al., In Press), we evaluated the association of depressive symptom clusters and smoking exposure accumulated over 25 years with CAC at Year 25 in the CARDIA study. We used a 14-item, 3-factor (negative affect, anhedonia, somatic symptoms) characterization of the Center for Epidemiologic Studies Depression (CES-D) scale (Carleton et al., 2013). Based on previous studies, we hypothesized that the somatic symptom cluster (Baune et al., 2012) and the negative affect cluster (Stewart et al., 2012), but not the anhedonia cluster, of cumulative depressive symptoms would interact with cumulative smoking exposure in association with CAC.

## Methods

### Study Design and Participants

Data from the CARDIA study were analyzed. Participants (N=5,115) were recruited in 1985–1986 (Year 0). Recruitment was stratified on gender (men and women), race (Black and White), age (18–24 or 25–30), education ( or > high school education), and study site (Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA). Participants completed follow-up assessments at Years 2, 5, 7, 10, 15, 20 and 25. Data from all exams were included in the present study. The study protocol was reviewed and approved by the IRB at each study center for each exam period. All participants completed written and signed informed consent to participate in all study procedures.

### Measures

**Smoking**—At Year 0, smoking was assessed by self-reported age of smoking initiation, current smoking status, and number of cigarettes smoked per day. Smoking status was subsequently assessed at each follow-up in-person exam and each annual telephone and participants were queried about how many cigarettes they currently smoked per day or when they quit smoking. From these data, a cumulative measure of smoking exposure (packyears: cigarette packs smoked per day × years smoking) was calculated for each participant from Year 0 to Year 25.

**Depressive symptoms**—Depressive symptoms were measured at Years 5, 10, 15, 20, and 25 using the Center for Epidemiologic Studies Depression (CES-D) scale (Radloff, 1977). We used the 14-item, 3-factor model conducted by Carleton et al. (2013), which was

validated in a variety of samples, and is more consistent with current diagnostic criteria for depressive episodes. Depressive symptom clusters include negative affect (i.e., depressed mood; items 3, 6, 14, and 18), anhedonia (i.e., absence of positive affect; items 4, 8, 12, and 16), and somatic symptoms (i.e., physical manifestations, such as fatigue and appetite changes; items 1, 2, 5, 7, 11, and 20). Each item is scored from 0 to 3 for a total possible score of 42. The total possible scores for each subscale are 12, 12, and 18 for negative affect, anhedonia, and somatic symptoms, respectively. To create a cumulative measure for each depressive symptom cluster, areas under the curves (AUCs) were estimated using a three-step procedure, as has been done previously (Auer, Vittinghoff, Yaffe, & et al., 2016; Yaffe et al., 2014). To simplify the interpretation of the AUCs, each value was divided by 20 (Year 5 to Year 25) to obtain time-weighted averages of the AUCs. This analytic strategy minimizes missing data and allows us to include all individuals with at least one CES-D score.

**Coronary artery calcification (CAC)**—At Year 25, 3,189 participants underwent imaging for CAC using an established imaging protocol (Carr et al., 2005). Using the Agatston scoring method (Agatston et al., 1990), CAC was categorized into absence (score =0) vs. presence (score >0) of CAC. We chose to analyze CAC as a dichotomous measure due to the small proportion of the sample with CAC >0, given their relatively young age (range: 43 to 55 years at Year 25). This method is consistent with previous studies evaluating the association between depressive symptoms and CAC (e.g., Stewart et al., 2012).

**Covariates**—Known CAC and CVD risk factors were included in all analytic models (Loria et al., 2007; Reis et al., 2013). Sociodemographic variables, determined at Year 0 and confirmed at subsequent exam years, included gender, race (White or Black), age (years), and education (years). We used a gender × race variable to control for the documented effect of gender by race on CAC (Loria et al., 2007). Clinical variables, measured at every exam year, included total cholesterol (mg/dL), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body mass index (BMI; kg/m<sup>2</sup>), and diabetes status. Diabetes was diagnosed by at least one of the following at any exam year: 1) fasting glucose ≥126 mg/dL, 2) 2-hour oral glucose tolerance test ≥200 mg/dL, 3) hemoglobin A1c ≥6.5%, and/or 4) use of diabetic medications. Behavioral variables, measured at every exam year, included physical activity (amount of moderate and vigorous physical activity, score derived from responses on the CARDIA Physical Activity History Questionnaire) (Jacobs, Hahn, Haskell, Pirie, & Sidney, 1989) and alcohol use (measured in drinkyears: alcoholic drinks per day × years drinking) (Pletcher et al., 2005). All covariates were measured cumulatively from Year 0 to Year 25, where available, to reflect the accumulation of risk that develops from continuous exposure.

## Data analysis

All participants who underwent screening for CAC at Year 25 were included in the analyses. We examined the characteristics of the sample stratified by CAC (=0 vs. >0) on all of the exposure variables using t-tests and chi-square analysis. We explored the distribution of depressive symptoms for the overall score and the three symptom clusters.

Logistic regression analyses were performed to evaluate the association between smoking exposure accumulated through Year 25, depressive symptoms accumulated through Year 25, and CAC at Year 25 ( $=0$  vs.  $>0$ ). We ran four models, one for each depressive symptom measure (negative affect, anhedonia, somatic symptoms, and CES-D total). All models included the respective smoking  $\times$  depressive symptom measure interaction, the main effect of smoking exposure, and the main effect of depressive symptoms, and were adjusted for the sociodemographic, clinical, and behavioral covariates. To probe significant interaction terms, we computed odd ratios at selected levels of packyears and depressive symptoms.

To evaluate whether one depressive symptom cluster  $\times$  smoking interaction would be associated with CAC above and beyond the other depressive symptom clusters, we ran a single model with all three depressive symptom clusters  $\times$  smoking interactions, including the main effects of smoking exposure, negative affect, anhedonia, and somatic symptoms and adjusted for the sociodemographic, clinical, and behavioral covariates.

## Results

### Sample characteristics

Of the 3,189 participants who underwent CAC screening at Year 25, 907 participants (28% of the sample) had any CAC at Year 25. Participants with CAC differed significantly on all exposure variables, except for depressive symptoms, compared to those without CAC (Table 1). Depressive symptomatology varied sufficiently between Year 5 and Year 25, with median (range) standard deviation values of 3.27 (20.51) for CES-D total, 1.19 (1.27) for negative affect, 1.73 (8.49) for anhedonia, and 1.52 (9.90) for somatic symptoms. The correlations between the depressive symptom clusters were relatively strong (negative affect and somatic symptoms  $r=0.782$ ; negative affect and anhedonia  $r=0.580$ ; anhedonia and somatic symptoms  $r=0.517$ ),  $ps<.001$ . The correlations between each depressive symptom cluster and cumulative smoking exposure were significant but weak (negative affect  $r=0.077$ ,  $p<.001$ ; anhedonia  $r=0.037$ ,  $p=.011$ ; somatic symptoms  $r=0.066$ ,  $p<.001$ ).

### Depressive symptoms subtypes, smoking exposure, and CAC

The depressive symptoms subscales  $\times$  smoking interactions were significant for somatic symptom cluster ( $p=.028$ ) and for the CES-D total ( $p=.017$ ), but not for negative affect cluster ( $p=.084$ ) or the anhedonia cluster ( $p=0.071$ ). In the negative affect cluster model, only the smoking main effect was significant ( $p<0.001$ ) and in the anhedonia cluster model, neither depressive symptoms nor smoking had significant main effects ( $ps>.05$ ).

Tables 2a, b, c, and d show the odds ratios computed at selected combinations of levels of packyears of smoking and negative affect, anhedonia, somatic, and CES-D total symptoms, respectively. Tables 2c and d show that higher cumulative scores on the somatic symptoms and the CES-D total scales were associated with higher odds of CAC  $>0$ , especially among participants with greater accumulation of smoking exposure. Specifically, relative to participants with 0 packyears and 0 somatic depressive symptoms, a 25% somatic symptom score (5 points out of 18) with smoking exposure levels of 10, 20, and 30 packyears were associated with ORs (95% CIs) of 1.62 (1.12–2.33), 2.43 (1.64–3.61), and 3.66 (2.34–5.72),

respectively, while a 50% somatic symptom score (9 points out of 18) with smoking exposure levels of 10, 20, and 30 packyears were associated with ORs (95% CIs) of 2.06 (1.08–3.93), 3.71 (1.81–7.57), and 6.68 (2.87–15.53), respectively (Table 2c). A similar but less pronounced pattern was observed for CES-D total (Table 2d).

### All depressive symptom clusters, smoking exposure, and CAC

In the model evaluating the relative associations between all three depressive symptom clusters with CAC, none of the interactions between depressive symptom clusters and smoking nor the main effects of depressive symptom clusters were associated with CAC >0 at Year 25, all  $p$ s > .05. Excluding all of the interactions, the main effect of smoking exposure was significantly associated with CAC (OR: 1.42, 95% CI: 1.30–1.55,  $p$  < .001), but none of the depressive symptom clusters main effects were significantly associated with CAC, all  $p$ s > .20.

## Discussion

In the present study, we evaluated the association between the interaction of cumulative depressive symptom clusters and cumulative smoking exposure in relation to CAC. Using data from the CARDIA study, we observed that somatic symptoms, but not negative affect or anhedonia, accumulated over 20 years interacted with smoking exposure accumulated over 25 years and was associated with significantly higher odds of CAC >0 at Year 25. Somatic symptoms and smoking exposure were synergistically associated with greater odds of having any CAC at Year 25. Our findings are largely consistent with previous studies indicating that somatic symptoms of depression are most strongly associated with cardiovascular disease risk and outcomes, compared to other depressive symptom clusters (Baune et al., 2012; Hawkins et al., 2014).

Specifically, for adults with mildly elevated somatic symptoms (score of 5 out of 18), we observed that 10, 20, and 30 packyears of smoking exposure were associated with 1.6, 2.4, and 3.7 higher odds of CAC >0, respectively, whereas among adults with moderately elevated somatic symptoms (score of 9 out of 18), 10, 20, and 30 packyears of smoking exposure were associated with 2.1, 3.7, and 6.7 higher odds of CAC >0, respectively. Thus, the association between somatic depressive symptoms and the odds of CAC was strongest among participants with the greatest levels of smoking exposure.

With growing evidence that depression may be an independent risk factor for CVD (Brunner et al., 2014; Nicholson et al., 2006; O’Neil, Fisher, Kibbey, Jacka, Kotowicz, Williams, Stuart, Berk, Lewandowski, Taylor, et al., 2016), further clarification of the nature of this relationship with the risk factors, such as smoking, is needed. Likewise, identification and clarification of the facets of depressive symptomatology (including the timing, severity, and symptom clusters) that are particularly relevant for CVD will be useful for risk prediction and targeted interventions. A strength of our study is the cumulative measures of depressive symptoms and smoking exposure, as cumulative measures are superior to concurrent measures in predicting CAC (Loria et al., 2007). In particular, these measurements better modeled the chronic nature of smoking and depression, as well as the synergistic accumulation of risk associated with CAC (Carroll et al., In Press).

The association between somatic depressive symptoms and CVD is supported among patients with prevalent CVD. For example, Hoen et al. (2010) found that each somatic symptom (e.g., changes in appetite, sleep problems) reported by patients with CVD was associated with 14% increased risk of cardiac events. Furthermore, this association has been shown to be specific to somatic symptoms. Among patients with stable CVD followed for an average of 3 years, somatic symptoms, but not cognitive symptoms, were associated with 30% greater odds of recurrent myocardial infarction or sudden cardiac death (Martens, Hoen, Mittelhaeuser, de Jonge, & Denollet, 2010). In a recent study, CVD patients with persistent somatic depressive symptoms, compared to those with persistent total depressive symptoms, were at 86% greater risk of mortality (Roest, Wardenaar, & de Jonge, 2016). Fewer studies have evaluated the negative affect or anhedonia symptom clusters in relation to CVD, though some have also observed significant associations between these symptom clusters and cardiac outcomes (e.g., Davidson et al., 2010; Pelle et al., 2011).

Regarding incident CVD, one study observed that the somatic cluster of depressive symptoms were associated with incident CVD events above and beyond the other clusters of depressive symptoms (Hawkins et al., 2014). Another study found that somatic cluster, but not other negative affect measures (i.e., anxiety, hostility, or anger), were associated with progression of atherosclerosis as measured by carotid intima-media thickness (Stewart, Janicki, Muldoon, Sutton-Tyrrell, & Kamarck, 2007). The association of depressive symptom subtypes with incident CVD remains an area for future research.

The dimensions of depression also have differential associations with smoking behaviors. For example, evidence indicates that somatic symptoms and negative affect are more strongly associated with smoking initiation (Leventhal, Ray, Rhee, & Unger, 2012), while anhedonia is a greater influence for maintaining nicotine dependence (Leventhal, Francione Witt, & Zimmerman, 2008; Mickens et al., 2011). In theory, depressed smokers with low hedonic capacity are more likely to mistake withdrawal relief they experience from smoking cigarettes as positive mood and pleasure (Leventhal & Zvolensky, 2015). If we had observed a significant association between the anhedonia by smoking interaction and CAC, it would have supported the idea that the association between depression and CVD is moderated by smoking. However, our findings suggest that depression may be an independent risk factor for CVD.

There are several proposed mechanisms by which depression, and certain depressive symptom clusters, is associated with CVD. One hypothesis for why the somatic symptoms cluster is associated with risk for CVD could be because when people are experiencing these somatic symptoms (e.g., fatigue, decreased appetite), they may be less likely to engage in other cardioprotective behaviors, such as increased physical activity or more moderate alcohol intake (Appleton et al., 2016). This would be consistent with the viewpoint that depression may increase risk for CVD primarily via behavioral mechanisms, including smoking (Baune et al., 2012). However, the models were all adjusted for these traditional behavioral risk factors, and these covariates did not negate the association between the smoking by somatic symptoms interaction with CAC. Therefore, while smoking may amplify the association between depressive symptoms and CVD, the behavior itself does not appear to wholly account for this association.

Some researchers have suggested that depression is an inflammatory disease (Berk et al., 2013; Miller & Raison, 2016), and some have hypothesized that this inflammatory response explains the association between depression and CVD (Poole, Dickens, & Steptoe, 2011). C-reactive protein (CRP), a systemic measure of inflammation, appears to be particularly related to certain somatic symptoms in depression (Case & Stewart, 2014; Hickman, Khambaty, & Stewart, 2014). For example, Copeland, Shanahan, Worthman, Angold, and Costello (2012) found that more depressive episodes was associated with higher levels of CRP. However, Smolderen et al. (2012) did not find any association between either somatic symptoms or cognitive symptoms with inflammatory levels in patients who had suffered a recent (<1 month) myocardial infarction. Cigarette smoking also increases systemic inflammation (USDHHS, 2010), which may explain the amplified association between depressive symptoms, and the somatic cluster in particular, and CVD. Further elucidating the mechanisms by which depression causes CVD, whether behavioral, biological, or both, may be helpful for developing treatments for these at-risk individuals.

Our results are inconsistent with those reported by Stewart et al. (2012) using data from the CARDIA study, where they reported that negative affect depressive symptoms, rather than the somatic symptoms cluster, held the strongest association with 5-year incidence of CAC. In addition to evaluating the interaction between depressive symptoms and smoking exposure, there are several differences between the Stewart et al. study and the present analysis. Our analytic design included more participants (3,189 vs. 2,171), a greater number of cases with CAC >0 (28% vs. 11%), and measures of accumulated exposures (Year 0 through Year 25 versus Year 15 only). Furthermore, our results are consistent with other studies that observed somatic symptoms to be the strongest predictor of incident CVD (Hawkins et al., 2014).

This study has some limitations. First, we cumulatively measured depressive symptoms from all available exams (Year 5 to Year 25), which does not allow us to evaluate the impact of timing, number, or pattern of depressive symptoms elevations. Second, we only evaluated 3 depressive symptom clusters, although other clusters have been studied previously (e.g., cognitive symptoms: Hamer et al., 2010). Finally, because the exam periods were several years apart, and our depressive symptoms measure evaluated symptoms over the previous two weeks, we may have missed some depressive symptom elevations. However, we used five assessments over 20 years, thereby minimizing missing data and most likely capturing individuals who were likely to have had elevated depressive symptoms.

This study is the first to evaluate how cumulative depressive symptom clusters interacted cumulative smoking exposure and associated with CAC. Our findings highlight the importance of considering different depressive symptom clusters not only as potential independent risk factors for CVD, but also in how these clusters may interact with traditional CVD risk factors, such as smoking. Understanding how the various facets of depression are associated with the well-established relationship between smoking and CVD risk has implications for developing targeted treatments for these high-risk patients.



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**Table 1**

Participant characteristics by Year 25 CAC status

Variable	CAC		p-value
	Agatston score =0 (n=2,282)	Agatston score >0 (n=907)	
<i>Gender × Race</i>			<.001
Black women, n (%)	743 (32.6%)	172 (19.0%)	
Black men, n (%)	391 (17.1%)	211 (23.3%)	
White women, n (%)	740 (32.4%)	150 (16.5%)	
White men, n (%)	408 (17.9%)	374 (41.2%)	
Age (years), mean (SD)	49.7 (3.7)	52.2 (3.2)	<.001
Education (years), median (IQR)	16 (4)	14 (4)	<.001
Cholesterol (mg/dL), median (IQR)	179.2 (32.6)	189.8 (34.5)	<.001
SBP (mmHg), median (IQR)	109.8 (12.3)	114.7 (12.4)	<.001
DBP (mmHg), median (IQR)	70.3 (8.9)	72.9 (8.8)	<.001
BMI (kg/m <sup>2</sup> ), median (IQR)	25.8 (6.6)	26.9 (6.7)	<.001
Diabetes, n (%)	264 (11.6%)	173 (19.1%)	<.001
Physical activity score, median (IQR)	5.7 (1.0)	5.8 (0.9)	<.001
Alcohol use <sup>a</sup> (drinkyears)	15.8 (23.5)	21.4 (29.9)	<.001
Smoking <sup>b</sup> (packyears), median (IQR)	5.9 (13.4)	11.7 (19.4)	<.001
<i>Depressive symptoms</i>			
Negative affect, median (IQR)	1.2 (1.7)	1.2 (1.8)	.550
Anhedonia, median (IQR)	3.3 (2.7)	3.4 (2.7)	.509
Somatic symptoms, median (IQR)	2.8 (2.3)	2.8 (2.3)	.700
CES-D total score, median (IQR)	7.6 (6.2)	7.7 (6.3)	.399

Year 25 values were measured or confirmed (gender, race, education), calculated (age), or measured cumulatively through Year 25 (total cholesterol, SBP, DBP, BMI, physical activity score, alcohol use, smoking, and depressive symptoms), for which the values are the time-weighted averages of AUC calculations. Score ranges for depressive symptom scales are: negative affect score (0–12), anhedonia score (0–12), somatic symptoms score (0–18), CES-D total score (0–42).

<sup>a</sup>Mean drinkyears among ever drinkers, N=1,751 (CAC=0: n=1217, CAC >0: n=534).

<sup>b</sup>Mean packyears among ever smokers, N=1,576 (CAC=0: n=1059, CAC >0: n=520).

Abbreviations: CAC, coronary artery calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CES-D, Centers for Epidemiologic Studies – Depression scale; SD, standard deviation; IQR, interquartile range; AUC, area under the curve.

Table 2

## a. Odds Ratio (95% Confidence Interval) of CAC &gt;0 at Year 25 for each smoking × negative affect depressive symptoms group

Smoking (Packyears)	Negative affect score		
	0	3	6
0	Ref	0.97 (0.74–1.26)	0.93 (0.55–1.59)
10	<b>1.30 (1.13–1.49)</b>	<b>1.43 (1.09–1.88)</b>	1.58 (0.94–2.66)
20	<b>1.69 (1.29–2.22)</b>	<b>2.12 (1.55–2.90)</b>	<b>2.67 (1.47–4.85)</b>
30	<b>2.20 (1.47–3.30)</b>	<b>3.15 (2.16–4.60)</b>	<b>4.50 (2.17–9.35)</b>

## b. Odds Ratio (95% Confidence Interval) of CAC &gt;0 at Year 25 for each smoking × anhedonia depressive symptoms group

Smoking (Packyears)	Anhedonia score		
	0	3	6
0	Ref	0.97 (0.77–1.22)	0.94 (0.60–1.49)
10	1.21 (0.99–1.47)	<b>1.32 (1.02–1.71)</b>	1.45 (0.93–2.27)
20	1.45 (0.97–2.17)	<b>1.80 (1.31–2.48)</b>	<b>2.23 (1.38–3.60)</b>
30	1.75 (0.96–3.20)	<b>2.45 (1.65–3.65)</b>	<b>3.43 (2.01–5.87)</b>

## c. Odds Ratio (95% Confidence Interval) of CAC &gt;0 at Year 25 for each smoking × somatic depressive symptoms group

Smoking (Packyears)	Somatic symptoms score		
	0	5	9
0	Ref	1.08 (0.75–1.55)	1.14 (0.59–2.21)
10	<b>1.20 (1.01–1.43)</b>	<b>1.62 (1.12–2.33)</b>	<b>2.06 (1.08–3.93)</b>
20	<b>1.44 (1.01–2.03)</b>	<b>2.43 (1.64–3.61)</b>	<b>3.71 (1.81–7.57)</b>
30	<b>1.72 (1.02–2.90)</b>	<b>3.66 (2.34–5.72)</b>	<b>6.68 (2.87–15.53)</b>

## d. Odds Ratio (95% Confidence Interval) of CAC &gt;0 at Year 25 for each smoking × total depressive symptoms group

Smoking (Packyears)	CES-D total score		
	0	11	21
0	Ref	1.01 (0.73–1.38)	1.01 (0.55–1.85)
10	1.16 (0.96–1.40)	<b>1.46 (1.06–2.02)</b>	1.81 (1.00–3.27)
20	1.35 (0.93–1.97)	<b>2.13 (1.49–3.04)</b>	<b>3.22 (1.68–6.18)</b>
30	1.57 (0.89–2.76)	<b>3.10 (2.06–4.65)</b>	<b>5.74 (2.67–12.35)</b>

**Bold** indicates significantly ( $p < .05$ ) greater odds of CAC >0 relative to CAC =0, centered on 0 drinkyears. All models were adjusted for sociodemographic, clinical, and behavioral covariates that are known risk factors for CAC and CVD: gender × race, age, education, total cholesterol, systolic blood pressure, diastolic blood pressure, body mass index, diabetes status, physical activity, alcohol use, and alcohol use × depressive symptoms. The depressive symptoms are indicated at 0, 25% of total score, and 50% of total score for each scale, where the possible range of scores are 0 to 12 for negative affect symptom scores, 0 to 12 for anhedonia symptom scores, 0 to 18 for somatic symptom scores, 0 to 42 for CES-D total scores.

Abbreviations: CAC, coronary artery calcification; CES-D, Centers for Epidemiologic Studies Depression scale; Ref, reference category.