HHS Public Access
Author manuscript
*Health Psychol*. Author manuscript; available in PMC 2018 February 01.

Published in final edited form as:
*Health Psychol*. 2017 February ; 36(2): 101–111. doi:10.1037/hea0000425.

# Interaction between Smoking and Depressive Symptoms with Subclinical Heart Disease in the CARDIA study

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## Abstract

**Objective—**Evaluate whether smoking exposure and depressive symptoms accumulated over 25 years are synergistically associated with subclinical heart disease, measured by coronary artery calcification (CAC).

**Methods—**Participants (baseline: 54.5% female; 51.5% Black; age range=18–30 years) were followed prospectively from 1985 to 2010 in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Smoking status was queried yearly from Year 0 to Year 25 to compute packyears of smoking exposure. Depressive symptoms were measured on the Center for Epidemiologic Studies Depression (CES-D) scale every five years to compute cumulative scores from Year 5 to Year 25. A three-level multinomial logistic regression was used to evaluate the association between cumulative smoking, cumulative depressive symptoms, and their interaction with moderate-risk CAC (score 1-99) and higher-risk CAC (score ≥100) compared to no CAC (score =0) at Year 25. Models were adjusted for sociodemographic, clinical, and behavioral covariates.

**Results—**Among 3,189 adults, the cumulative smoking x depressive symptoms interaction was not significant for moderate-risk CAC ($p$=.057), but was significant for higher-risk CAC ($p$=.001). For adults with a 30-packyear smoking history, average CES-D scores 2, 10, and 16 were respectively associated with odds ratios (95% confidence intervals) 3.40 (2.36–4.90), 4.82 (3.03–7.66), and 6.25 (3.31–11.83) for higher-risk CAC (all $p$s<.05).

This manuscript was reviewed by CARDIA for scientific content. A full list of participating investigators and institutions can be found at http://www.cardia.dopm.uab.edu, as well as access to publications and information concerning collaboration and data sharing of CARDIA resources. This manuscript is based on a thesis submitted in partial fulfillment for the degree of Master of Science at Northwestern University Feinberg School of Medicine. Preliminary results were presented at the Society for Behavioral Medicine Scientific Conference in San Antonio on April 24, 2015.

**Conclusion—**Cumulative smoking exposure and cumulative depressive symptoms have a synergistic association with subclinical heart disease, where higher lifetime smoking exposure and depressive symptoms are associated with greater odds of CAC.

**Keywords**

smoking; depression; coronary artery calcification; atherosclerosis; multiple risk factors

Heart disease is the leading cause of death in the United States and worldwide (CDC, 2011; WHO, 2013), and many modifiable lifestyle factors, such as smoking, physical activity, diet, and obesity, are causally linked to heart disease. More recently, psychological conditions, most notably depression, have been shown to predict worse outcomes among individuals with heart disease (Lichtman et al., 2014), and there is growing evidence that depression also predicts incident heart disease (Nicholson, Kuper, & Hemingway, 2006; O'Neil et al., 2016). These factors have primarily been addressed in isolation in the prevention and treatment of heart disease, even though these conditions commonly co-occur and may interactively increase risk for heart disease.

For instance, smoking and depression are both risk factors for heart disease (Baune et al., 2012; USDHHS, 2014), the two conditions are highly comorbid (Pratt & Brody, 2010), and the presence of one interferes with treatment of the other (Dodd et al., 2010; Hitsman et al., 2013; Jamal, Willem Van der Does, Cuijpers, & Penninx, 2012). In a study of over 8,000 male twins, a shared genetic basis for daily smoking, nicotine dependence, and depression was observed, with stronger correlations between monozygotic compared to dizygotic twins (Lyons et al., 2008). There is further evidence that cigarette smoking predicts depression and greater severity of depressive symptoms (Boden, Fergusson, & Horwood, 2010), as well as that depression predicts initiation of and progression to daily smoking (Munafo, Hitsman, Rende, Metcalfe, & Niaura, 2008).

Understanding the potential synergistic association between smoking and depression with heart disease could be improved by examining the underlying factors that indicate risk for future heart disease or cardiac events. Coronary artery calcification (CAC) is a measure of subclinical atherosclerosis and is the best known predictor of future heart disease in asymptomatic individuals (Greenland et al., 2007; Shaw, Raggi, Schisterman, Berman, & Callister, 2003). Smoking has a dose-dependent association with CAC (Rasmussen et al., 2013), and smokers with elevated CAC are more likely to suffer cardiac death compared to their nonsmoking counterparts with equal levels of CAC (Shaw, Raggi, Callister, & Berman, 2006).

Persistent depression is associated with subclinical heart disease, even after adjusting for smoking status (Agatisa et al., 2005; Hamer, Kivimaki, Lahiri, Marmot, & Steptoe, 2010; I. Janssen et al., 2016; Matthews, Chang, Sutton-Tyrrell, Edmundowicz, & Bromberger, 2010), and relative risk of CAC progression increases for each incremental increase in depressive symptoms (Imke Janssen et al., 2011), though the latter study did not adjust for smoking status. In a prior study using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, Stewart et al. (2012) observed that higher depressive symptoms were associated with greater odds of 5-year incidence of CAC. While these studies have controlled for smoking status, no studies have evaluated the interaction between smoking and depression in relation to subclinical measures of heart disease.

The purpose of the present study was to evaluate whether smoking exposure and depressive symptoms accumulated over 25 years were associated with greater odds of CAC. We hypothesized that these two risk factors would synergistically interact, such that higher levels of cumulative smoking exposure and cumulative depressive symptoms would be associated with greater odds of CAC beyond the independent associations of smoking and depressive symptoms.

## Methods

### Study Design and Participants

The Coronary Artery Risk Development in Young Adults (CARDIA) study was designed to examine the development and progression of heart disease in Black and White men and women sampled from four sites in the U.S.: Birmingham, AL; Minneapolis, MN; Chicago, IL; and Oakland, CA. Sampling occurred such that the participants within and across sites comprised nearly equal parts in race (Black or White), gender (man or woman), education (less than/equal to or more than high school education), and age (18–24 or 25–30 years). The study was approved by the institutional review board at each site and informed signed consent was obtained from all participants. The initial sample (N=5,115) was recruited in 1985–1986 (Year 0). Participants were then invited to complete follow-up exams at Years 2, 5, 7, 10, 15, 20 and 25 with 91%, 86%, 81%, 79%, 74%, 72%, and 72% retention, respectively. Data were collected on a variety of measures related to heart health, from self-report questionnaires to physical exams to imaging measures. The timing of exams and measures are presented in Supplemental Material (Table S1). The analytic design used variables through Year 25, with the outcome being CAC at Year 25.

### Measures

**Smoking exposure—**Cigarette smoking was evaluated during each in-person CARDIA visit and at yearly contacts over the phone between CARDIA visits. At baseline, participants were asked “Altogether, how many years have you smoked cigarettes regularly?” Smoking status at each follow-up contact was measured by the question “Do you smoke at least 5 cigarettes per week, almost every week?” If yes, participants were then asked “How many cigarettes do you smoke per day on average?” When applicable, at follow-up exams participants were asked, “How many years ago did you stop?” These data were used to estimate cumulative lifetime exposure to cigarettes in terms of packyears, where 1 packyear of smoking exposure is equivalent to smoking 1 pack of cigarettes per day for one year. (Auer et al., 2014; Pletcher, Vittinghoff, Kalhan, & et al., 2012).

**Depressive symptoms—**Depressive symptoms were measured using the 20-item Center for Epidemiologic Studies Depression (CES-D) scale at exam Years 5, 10, 15, 20 and 25. The CES-D asks about the severity of symptoms an individual has experienced over the past two weeks, and each item is scored from 0 (rarely or none of the time) to 3 (most or all of the time), for a total possible score between 0 and 60, where scores ≥16 are indicative of significantly elevated depressive symptoms (Radloff, 1977). A cumulative score was calculated for depressive symptoms, as described in detail below (Data Analysis).

**Coronary artery calcification—**CAC imaging occurred at Year 25, when participants were in middle adulthood (42 to 59 years old). Of those who completed the Year 25 exam, 3,189 participants (91.1% of the exam year sample) participated in the CAC screening. CAC scores were calculated using the validated method originally described by Agatston (Agatston et al., 1990). CAC screening demonstrated acceptable agreement between the two scans and very high agreement for both intra- and inter-rater reliability (Carr et al., 2005). CAC outcomes were categorized into none (lowest risk; Agatston score=0), moderate-risk (Agatston score 1-99), versus higher-risk (Agatston score ≥100) CAC, and also analyzed as continuous scores among individuals with CAC >0 (described and presented in Supplemental Material).

**Covariates—**Year 25 sociodemographic, clinical, and behavioral variables that have been shown to be associated with CAC and heart disease were included in the analysis models as covariates (Allen et al., 2014; Bild et al., 2001; Loria et al., 2007; Reis et al., 2013; Yan et al., 2006).

Sociodemographic variables included gender (male versus female), race (White versus Black), age (in years), and education (in years). To adjust for the race by gender effect on heart disease and CAC (i.e., higher prevalence of CAC among White males: Loria et al., 2007), these variables were included in the model as a single, 4-level gender (male or female) by race (White or Black) interaction variable, where White women was the reference category. These variables were determined at baseline and confirmed at Year 2 (gender and race) or queried at each subsequent exam (age and education).

Clinical variables were total cholesterol (mg/dL), systolic blood pressure (SBP; mmHg), diastolic blood pressure (DBP; mmHg), body mass index (BMI; kg/m$^2$), and diabetes status. Total cholesterol, SBP, DBP, and BMI were modeled continuously. Diabetes was dichotomized (yes=1, no=0), diagnosed by at least one of the following: 1) fasting glucose ≥126 mg/dL, 2) 2-hour oral glucose tolerance test result ≥200 mg/dL, 3) hemoglobin A1c (HbA1c) ≥6.5%, and/or 4) current use of diabetic medications.

Behavioral variables were alcohol use and physical activity, measured at each exam year through Year 25. Alcohol use was measured at each exam by the question, “Did you drink any alcoholic beverages in the past year?” If a participant answered yes, he or she was then queried as to the number of drinks of beer, wine, and hard liquor consumed in a typical week. From these responses, a continuous, cumulative drinkyears variable was calculated by multiplying the average daily alcohol use by the number of years drinking (Pletcher et al., 2005). A physical activity intensity score was derived from the CARDIA Physical Activity History Questionnaire (Jacobs, Hahn, Haskell, Pirie, & Sidney, 1989), which queries participants about the time spent performing vigorous and moderate intensity physical activities over the past 12 months.

### Data analysis

All participants who underwent CAC screening at Year 25 were included in the present analyses. Because heart disease risk factors tend to change and accumulate over time, cumulative exposure to the independent variables were measured by estimating areas under the curves (AUCs) using a three-step procedure, as has been done previously (Auer, Vittinghoff, Yaffe, & et al., 2016; Yaffe et al., 2014). AUCs were estimated for depressive symptoms (CES-D scores), total cholesterol, SBP, DBP, BMI, and physical activity. First, the population mean trajectory of each variable was estimated using linear mixed models (further details are provided in the Supplemental Material). Second, participant-specific trajectories were calculated for each variable by combining the random effects best linear unbiased predictions (BLUPs) with the fixed effect estimates. Finally, AUCs were calculated over the interval from baseline (Year 0) to the outcome exam (Year 25). To simplify the interpretation of the AUCs, each value was divided by 25 to obtain time-weighted averages (TWA) of the AUCs, corresponding to the number of years of observation from the first exam (Year 0) through the final exam (Year 25). For depressive symptoms, the AUCs were divided by 20, as the CES-D was given starting at the Year 5 exam. Further detail is provided in the Supplemental Material. To compute cumulative exposures for smoking and alcohol use, backward and forward linear imputation was used to interpolate missing data between visits. By using mixed models for computing AUCs, which use maximum likelihood estimations, it was unnecessary to compute missing data between visits for those variables (Vittinghoff, Glidden, Shiboski, & McCulloch, 2012).

A 3-level multinomial logistic regression was run to evaluate CAC 1-99 or CAC ≥100 compared to CAC =0. First, the smoking and depressive symptoms main effects terms were included, as well as the gender x race, education, BMI, total cholesterol, SBP, DBP, diabetes, physical activity, and alcohol use covariates (Model 1). Second, the model was adjusted for the smoking x depressive symptoms interaction (Model 2). Finally, to more fully examine the association between depressive symptoms with CAC among individuals with different levels of smoking exposure, interactions between depressive symptoms and the clinical and behavioral covariates were individually added and removed to assess for changes in the association between the smoking x depressive symptoms interaction with CAC (Model 3). A likelihood ratio test was used to evaluate for significant improvements for each model adjustment.

In sensitivity analyses, we examined the effects of using concurrent, Year 25 measures of smoking (cigarettes per day at Year 25) and depressive symptoms (CES-D at Year 25). First, we further adjusted the primary multinomial logistic regression model for Year 25 smoking and Year 25 depressive symptoms, and their interaction. Second, the 3-level multinomial logistic regression analysis was performed using only concurrent exposures, including Year 25 smoking, Year 25 depressive symptoms, their interaction, and Year 25 measures of covariates (i.e., cholesterol, SBP, DBP, BMI, diabetes status, physical activity score, past 24-hour alcohol use, and the sociodemographic covariates). To test the assumption that measuring cumulative exposures of variables would significantly improve the model predicting CAC, a likelihood ratio test was used to compare the fit of the these models with the fit of the primary, cumulative exposures-only model. Analyses were conducted using STATA 13. A threshold of $p<.05$ was used to determine significance.

## Results

### Description of the sample

The number of participants who underwent CAC screening at Year 25 was 3,189. Of the total sample, 907 participants (28.4%) had any CAC (Agatston score >0) at Year 25, where 597 participants had moderate-risk CAC (1-99) and 310 participants had higher-risk CAC (≥100). Agatston scores ranged from 0 to 5950, with a mean score of 38 (SD=193). The characteristics of the sample by CAC status are presented in Table 1. Significant correlations were observed between cumulative smoking packyears and Year 25 cigarettes per day ($r$=0.73) and between cumulative depressive symptoms and Year 25 CES-D score ($r$=0.77), $p$s<.001. For smoking, less than 1.0% of the values were missing across the exam years. For depression, 1.5% of the values were missing across the exam years. Further information about missing data are provided in Supplemental Material (Table S2).

### Cumulative exposures smoking x depressive symptoms interaction and CAC at Year 25

The odds ratios (ORs) for smoking are representative of higher odds per 10 packyears of smoking. The odds ratios for depressive symptoms are representative higher odds per each 16 points in the TWA-AUC CES-D score. In Model 1, smoking was significantly associated with CAC 1-99 (OR: 1.38, 95% CI: 1.25–1.53) and CAC ≥100 (OR: 1.50, 95% CI: 1.33–1.70), $p$s<.05, whereas depressive symptoms were not significantly associated with either level of CAC relative to CAC =0, $p$s>.05. In Model 2, the smoking x depressive symptoms interaction term was significant for CAC 1-99 and CAC ≥100, $p$s<.05 (see Table 2 for full model results). The likelihood ratio test did not indicate significant improvement in Model 2 relative to Model 1, $p$=.057.

For both CAC 1-99 and CAC ≥100, among participants with packyears=0 we did not observe an association between depressive symptoms and CAC. In contrast, among participants with packyears >0, higher levels of depressive symptoms accumulated over 25 years were associated with greater odds of CAC. For CAC 1-99 (Table 3a), this finding was observed only among participants with higher smoking exposure (packyears=30; TWA-AUC CES-D score of 2 OR: 2.60, 95% CI: 1.93–3.50; TWA-AUC CES-D score of 10 OR: 3.28, 95% CI: 2.20–4.90; TWA-AUC CES-D score of 16 OR: 3.91, 95% CI: 2.25–6.81). Among participants with packyears=10, on the other hand, higher levels of cumulative depressive symptoms were not associated with greater odds of CAC 1-99. For CAC ≥100 (Table 3b), higher depressive symptoms were associated with greater odds of CAC at all levels of smoking exposure (packyears >0), and this association was stronger at higher levels of smoking exposure (packyears=30; TWA-AUC CES-D score of 2 OR: 3.40, 95% CI: 2.36–4.90; TWA-AUC CES-D score of 10 OR: 4.82, 95% CI: 3.03–7.66; TWA-AUC CES-D score of 16 OR: 6.25, 95% CI: 3.31–11.83).

### Cumulative exposures smoking x depressive symptoms interaction and CAC at Year 25, with alcohol use x depressive symptoms interaction

To examine potential moderating factors that may explain why depression was associated with CAC among participants with packyears >0, but not among participants with packyears=0, the interactions between depressive symptoms and the clinical and behavioral covariates were included in the model. Only the alcohol use x depressive symptoms interaction was found to have a modifying influence on the association between depressive symptoms and CAC (Model 3). The alcohol use x depressive symptoms interaction was significant for CAC 1-99, $p$=.048, but not for CAC ≥100, $p$=.379. The smoking x depressive symptoms interaction was no longer significant for CAC 1-99 ($p$=.057), but remained significant for CAC ≥100, $p$=.001 (full model results presented in Table 4). Likelihood ratio tests indicated that Model 3 was not a significant improvement relative to Model 2, $p$=.051, but Model 3 was a significant improvement relative to Model 1, $p$=.019.

The interaction of smoking x depressive symptoms associated with CAC 1-99 was more evident for smokers (packyears >0) who did not drink alcohol (drinkyears=0, Table 5a) compared to those who consumed moderate levels of alcohol (drinkyears=8, Table 5b). In fact, among participants with no smoking history (packyears=0) and a moderate history of alcohol use (drinkyears=8), odds of CAC 1-99 were significantly lower among participants with elevated depressive symptoms than those without (TWA-AUC CES-D score of 2 OR: 0.96, 95% CI: 0.92–1.00; TWA-AUC CES-D score of 10 OR: 0.80, 95% CI: 0.66–0.98; TWA-AUC CES-D score of 16: 0.70, 95% CI: 0.51–0.97, $p$s<.05).

For CAC ≥100, the interaction of smoking x depressive symptoms was observed for all participants with packyears >0, whether they drank alcohol (Table 5d) or not (Table 5c). Specifically, the combination of high smoking exposure (30 packyears) and clinically elevated depressive symptoms (TWA-AUC CES-D score of 16) was associated with the highest odds of CAC for both 0 drinkyears (OR: 9.10, 95% CI: 3.97–20.88, $p$<.001) and 8 drinkyears (OR: 7.38, 95% CI: 3.69–14.79, $p$<.001).

### Year 25 smoking x depressive symptoms interaction and CAC at Year 25

When the primary model was adjusted for the Year 25 measures of smoking, depressive symptoms, and the smoking x depressive symptoms interaction, the only significant association between these Year 25 measures and CAC was observed between Year 25 smoking with CAC 1-99 (Table S3). The cumulative smoking x depressive symptoms interactions remained significant for both CAC 1-99 and CAC ≥100 (relative to CAC =0; $p$s<.05), and there was not a significant improvement in model fit by including these Year 25 measures ($R^2$=15.9% vs. 16.1%), $p$=.368.

In the 3-level multinomial logistic regression model evaluating the association between only Year 25 exposures with CAC 1-99 and CAC ≥100, relative to CAC =0, the Year 25 smoking x depressive symptoms interaction was not significant for CAC 1-99 or CAC ≥100 at Year 25, $p$s>.05 (Table S4). Covariate associations were largely similar between the Year 25 exposures model and the cumulative exposures model for CAC 1-99. For CAC ≥100, the Year 25 exposures model differed from the cumulative exposures model on several variables:

diabetes status, education (inverse), and DBP (inverse) were significantly associated with CAC, whereas total cholesterol was not associated with CAC in the Year 25 exposures model. The likelihood ratio tests showed that the cumulative exposures model explained significantly more of the variance ($R^2$=15.9% of variance explained) compared to the Year 25 exposures model ($R^2$=11.8%), $p$<.001, a 35% relative improvement in the model fit.

## Discussion

In a large, diverse sample, we tested the hypothesis that chronic smoking exposure and elevated depressive symptoms over 25 years would have an interactive association with subclinical heart disease. The hypothesized association between higher levels of depressive symptoms with greater odds of both moderate-risk and high-risk CAC was observed among all participants with a history of smoking exposure. In both instances, the association between depressive symptoms and CAC was strongest among adults with greater smoking exposure compared to adults with less smoking exposure. The observed associations among cumulative smoking, depressive symptoms, and CAC were largely independent of other sociodemographic, clinical, and behavioral factors associated with CAC and heart disease.

Among adults with a 10-packyear smoking history, those with minimal depressive symptoms (average CES-D score=2), compared to those with clinically elevated depressive symptoms (average CES-D score=16), did not have greater odds of moderate-risk CAC. However, among adults with a 30-packyear smoking history, minimal depressive symptoms versus those with clinically elevated depressive symptoms were associated with 2.60 and 3.91 greater odds of moderate-risk CAC, respectively, relative to adults with no smoking history and no depressive symptoms. For higher-risk CAC, a higher level of accumulated depressive symptoms was associated with CAC at all levels of smoking exposure (packyears >0). Among individuals with a 10-packyear smoking history, minimal depressive symptoms and clinically elevated depressive symptoms were associated with 1.50 and 1.84 greater odds, respectively, of higher-risk CAC. Among adults with a 30-packyear smoking history, minimal depressive symptoms and clinically elevated depressive symptoms were respectively associated with 3.40 and 6.25 greater odds of higher-risk CAC.

When examining whether other health-related behaviors moderated this association, we observed an inverse association between depressive symptoms and moderate-risk CAC among participants without any smoking history and a moderate history of alcohol use. Specifically, the odds of moderate-risk CAC among non-smokers and moderate drinkers were lower among individuals with elevated depressive symptoms; the association between alcohol use and moderate-risk CAC was not significant. Given the association between depressive disorders and alcohol use (Brière, Rohde, Seeley, Klein, & Lewinsohn, 2014; Grant & Harford, 1995), one speculative hypothesis is that depressed adults who do not smoke may be more likely to engage in alcohol use as a coping behavior (Holahan, Moos, Holahan, Cronkite, & Randall, 2003; Young-Wolff, Kendler, Sintov, & Prescott, 2009), which appears to have a cardioprotective effect at moderate levels (Mukamal et al., 2003; Poli et al., 2013).

Using cumulative measures of smoking and depressive symptoms, as well as covariates, assessed over 25 years explained significantly more of the variance than using concurrent Year 25 measures alone, improving the relative model fit by 35%. This finding is consistent with previous studies showing that smoking is a dose-dependent predictor of CAC (Loria et al., 2007; Rasmussen et al., 2013), where higher levels of smoking accumulated over 25 years was associated with greater odds of CAC at Year 25. Perhaps more importantly, this finding supports the hypothesis that CAC development is related to long-term elevated depressive symptoms or chronic major depressive disorder (Agatisa et al., 2005; Hamer et al., 2010; Matthews et al., 2010), rather than a current symptom profile (Devantier et al., 2013; Diez Roux et al., 2006). A previous analysis of CARDIA data, however, found an association between depressive symptoms at Year 15 and 5-year incident CAC using the CARDIA study data (Stewart et al., 2012). Clinically, these findings suggest that gathering a thorough history of smoking (e.g., number of years smoking) and depression (e.g., number and severity of depressive episodes) may improve understanding of the influence of depression on CVD.

The association between smoking and depression is well-established (Lyons et al., 2008; Munafo et al., 2008). Numerous mechanisms have been proposed to explain how smoking (USDHHS, 2010) and depression (Davidson, 2012) separately promote atherosclerosis and, ultimately, heart disease. Several of the proposed biological (e.g., systemic inflammation, endothelial dysfunction, and oxidative stress) and behavioral (e.g., physical inactivity and excessive alcohol use) mechanisms for the association between smoking and heart disease overlap with those relating depression and heart disease (Carney, Freedland, Miller, & Jaffe, 2002; Freedland, Carney, & Skala, 2005). For example, one proposed hypothesis is that depression causes dysfunction in the anti-inflammatory response (Miller, Cohen, & Ritchey, 2002; Stewart, Rand, Muldoon, & Kamarck, 2009). Therefore, when an inflammatory response is prompted by smoking (van der Vaart, Postma, Timens, & Ten Hacken, 2004), depressed adults compared to non-depressed adults may have a greater and/or more prolonged inflammatory response. Over time, this continuously augmented inflammation among depressed adults who smoke could accelerate the progression of atherosclerosis (Ridker, Hennekens, Buring, & Rifai, 2000). Smoking cessation is associated with decreases in depression, anxiety, and stress, and with increases in quality of life and positive affect (Taylor et al., 2014). Therefore, treatment that targets comorbid smoking and depression to decrease cardiovascular disease and improve cardiovascular health may be a fruitful area for future research.

A strength of this study is the use of longitudinal data to assess the interaction of key heart disease risk factors (i.e., smoking and depressive symptoms) over a 25-year follow-up period rather than a snapshot of concurrent symptoms or retrospective reports. Our study utilized measures of current smoking and depressive symptomatology at multiple exams over 25 or 20 years, respectively, which has been shown to be more accurate than retrospective reporting, particularly with regard to self-evaluation of mood intensity (Schwarz, 2007). By measuring cumulative smoking and repeatedly evaluating current depressive symptoms, we were able to model the chronicity of smoking and depressive symptoms over time. With regard to depressive symptoms, our results are similar to those reported by Hamer et al. (2010) and I. Janssen et al. (2016) in that the authors observed that persistent episodes, but not one episode of elevated depressive symptoms, predicted CAC. In the Hamer et al. study, however, the authors only evaluated cognitive depressive symptoms rather than a more global measure such as that used in the present study, and both studies measured number of episodes with elevated depressive symptomatology rather than using a cumulative measure of depressive symptoms over time.

The sample size and sampling procedures in the CARDIA study permit generalizability of findings to middle-aged adults in the U.S. The prevalence of Year 25 smoking in this sample (18%) is consistent 2010 reports of U.S. smoking prevalence (Garrett, Dube, Trosclair, Caraballo, & Pechacek, 2011). The prevalence of depression in this sample (40%) is consistent with estimates of lifetime prevalence of self-reported depression (Kruijshaar et al., 2005), though higher than lifetime prevalence estimates of major depressive disorder diagnosis (Kessler et al., 2003).

One limitation of our study was that the rate of moderate-risk CAC in this sample was low (28%), and the distribution of scores >0 was non-normal. Therefore, our interpretation about the amount of CAC among individuals with any CAC may be limited. However, many other studies, including those conducted with CARDIA data, have dichotomized CAC because these data have a large positive skew. Moreover, presence versus absence of CAC in younger adults, such as those in the CARDIA sample, is more indicative of poor heart disease outcomes compared to older individuals with equal levels of CAC (Kondos et al., 2003). Secondly, although using the AUC analyses for smoking and depressive symptoms allowed us to model the cumulative burden of smoking and depression over time, this approach does not permit us to explore the association with patterns of smoking or depression occurring over the course of the study and CAC. Future studies could explore these aspects (e.g., using latent growth curve analyses).

Future studies should examine potential mechanisms (biological and behavioral) for the smoking by depression interaction in healthy individuals to further understanding about how smoking and depression synergistically increase heart disease risk. In addition, the interaction between smoking and depression should be examined for its association with clinical heart disease (e.g., fatal and non-fatal myocardial infarction or stroke) to further elucidate the degree and specificity of the interactive effect of these two risk conditions on primary heart disease.

Among adults with an extensive smoking history, elevated depressive symptoms appears to be a particularly strong risk factor for subclinical heart disease. This has implications for treatment, where depressed adults who smoke may experience the greatest cardiovascular benefits if these two modifiable risk factors are addressed concurrently. Moreover, accounting for the accumulation of smoking and depression over 25 years improved prediction of Year 25 CAC compared to concurrent measurements of smoking status and depressive symptoms status, underscoring the need to gather a complete history of smoking and depression among patients at risk for heart disease. Understanding how key risk factors interact to influence the onset and progression of heart disease may serve to improve the timing and efficacy of heart disease prevention efforts. Future studies should to continue to examine how smoking, depression, and other behavioral factors interact at the subclinical level of heart disease to more fully elucidate the mechanisms of action for these risk factors on heart health, which has implications for preventing and treating modifiable risk factors for heart disease.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

The Coronary Artery Risk Development in Young Adults Study (CARDIA) is supported by the National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (HHSN268201300025C, HHSN268201300026C), Northwestern University (HHSN268201300027C), University of Minnesota (HHSN268201300028C), Kaiser Foundation Research Institute (HHSN268201300029C), and Johns Hopkins University School of Medicine (HHSN268200900041C). This project was also supported in part by NHLBI through (R01-HL098445) to Vanderbilt University and Wake Forest University. The funding agency had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; and preparation, review, or approval of this manuscript.

## References

Agatisa PK, Matthews KA, Bromberger JT, Edmundowicz D, Chang YF, Sutton-Tyrrell K. Coronary and aortic calcification in women with a history of major depression. Archives of Internal Medicine. 2005; 165(11):1229–1236. DOI: 10.1001/archinte.165.11.1229 [PubMed: 15956001]

Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. Journal of the American College of Cardiology. 1990; 15(4):827–832. [PubMed: 2407762]

Allen NB, Siddique J, Wilkins JT, Shay C, Lewis CE, Goff DC, … Lloyd-Jones DM. Blood pressure trajectories in early adulthood and subclinical atherosclerosis in middle age. The Journal of the American Medical Association. 2014; 311(5):490–497. DOI: 10.1001/jama.2013.285122 [PubMed: 24496536]

Auer R, Vittinghoff E, Kiefe C, Reis JP, Rodondi N, Khodneva YA, … Pletcher MJ. Change in physical activity after smoking cessation: the Coronary Artery Risk Development in Young Adults (CARDIA) study. Addiction. 2014; 109(7):1172–1183. DOI: 10.1111/add.12561 [PubMed: 24690003]

Auer R, Vittinghoff E, Yaffe K, et al. Association between lifetime marijuana use and cognitive function in middle age: The coronary artery risk development in young adults (CARDIA) study. JAMA Internal Medicine. 2016; doi: 10.1001/jamainternmed.2015.7841

Baune BT, Stuart M, Gilmour A, Wersching H, Heindel W, Arolt V, Berger K. The relationship between subtypes of depression and cardiovascular disease: A systematic review of biological models. Translational Psychiatry. 2012; 2:e92.doi: 10.1038/tp.2012.18 [PubMed: 22832857]

Bild DE, Folsom AR, Lowe LP, Sidney S, Kiefe C, Westfall AO, … Rumberger J. Prevalence and correlates of coronary calcification in black and white young adults: the Coronary Artery Risk Development in Young Adults (CARDIA) Study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2001; 21(5):852–857.

Boden JM, Fergusson DM, Horwood LJ. Cigarette smoking and depression: Tests of causal linkages using a longitudinal birth cohort. The British Journal of Psychiatry. 2010; 196(6):440–446. DOI: 10.1192/bjp.bp.109.065912 [PubMed: 20513853]

Brière FN, Rohde P, Seeley JR, Klein D, Lewinsohn PM. Comorbidity between major depression and alcohol use disorder from adolescence to adulthood. Comprehensive Psychiatry. 2014; 55(3):526–533. DOI: 10.1016/j.comppsych.2013.10.007 [PubMed: 24246605]

Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. Journal of Psychosomatic Research. 2002; 53(4): 897–902. [PubMed: 12377300]

Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR, … Detrano RC. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: Standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. Radiology. 2005; 234(1):35–43. DOI: 10.1148/radiol.2341040439 [PubMed: 15618373]

CDC. Prevalence of coronary heart disease - United States, 2006–2010. Morbidity and Mortality Weekly Reports. 2011; 60(40):1377–1381.

Davidson KW. Depression and coronary heart disease. International Scholarly Research Notices Cardiology. 2012; 743813(10):22.

Devantier TA, Norgaard BL, Sand NP, Mols RE, Foldager L, Diederichsen AC, … Videbech P. Lack of correlation between depression and coronary artery calcification in a non-selected Danish population. Psychosomatics. 2013; 54(5):458–465. DOI: 10.1016/j.psym.2013.01.005 [PubMed: 23414849]

Diez Roux AV, Ranjit N, Powell L, Jackson S, Lewis TT, Shea S, Wu C. Psychosocial factors and coronary calcium in adults without clinical cardiovascular disease. Annals of Internal Medicine. 2006; 144(11):822–831. [PubMed: 16754924]

Dodd S, Brnabic AJ, Berk L, Fitzgerald PB, de Castella AR, Filia S, … Berk M. A prospective study of the impact of smoking on outcomes in bipolar and schizoaffective disorder. Comprehensive Psychiatry. 2010; 51(5):504–509. [PubMed: 20728008]

Freedland KE, Carney RM, Skala JA. Depression and smoking in coronary heart disease. Psychosomatic Medicine. 2005; 67(Suppl 1):S42–46. DOI: 10.1097/01.psy.0000162255.55629.9c [PubMed: 15953800]

Garrett BE, Dube SR, Trosclair A, Caraballo RS, Pechacek TF. Cigarette smoking - United States, 1965–2008. Morbidity and Mortality Weekly Reports Surveillance Summaries. 2011; 14(60):109–113.

Grant BF, Harford TC. Comorbidity between DSM-IV alcohol use disorders and major depression: Results of a national survey. Drug and Alcohol Dependence. 1995; 39(3):197–206. DOI: 10.1016/0376-8716(95)01160-4 [PubMed: 8556968]

Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM. … Society of Cardiovascular Computed Tomography. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: A report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography). Circulation. 2007; 115(3):402–426. [PubMed: 17220398]

Hamer M, Kivimaki M, Lahiri A, Marmot MG, Steptoe A. Persistent cognitive depressive symptoms are associated with coronary artery calcification. Atherosclerosis. 2010; 210(1):209–213. [PubMed: 20153471]

Hitsman B, Papandonatos GD, McChargue DE, DeMott A, Herrera MJ, Spring B, … Niaura R. Past major depression and smoking cessation outcome: A systematic review and meta-analysis update. Addiction. 2013; 108(2):294–306. DOI: 10.1111/add.12009 [PubMed: 23072580]

Holahan CJ, Moos RH, Holahan CK, Cronkite RC, Randall PK. Drinking to cope and alcohol use and abuse in unipolar depression: a 10-year model. Journal of Abnormal Psychology. 2003; 112(1):159–165. [PubMed: 12653424]

Jacobs DR, Hahn LP, Haskell WL, Pirie P, Sidney S. Validity and reliability of a short physical activity history: CARDIA and the Minnesota Heart Health Program. Journal of Cardiopulmonary Rehabilitation. 1989; 9:448–459.

Jamal M, Willem Van der Does AJ, Cuijpers P, Penninx BW. Association of smoking and nicotine dependence with severity and course of symptoms in patients with depressive or anxiety disorder. Drug and Alcohol Dependence. 2012; 126(1–2):138–146. [PubMed: 22633368]

Janssen I, Powell LH, Matthews KA, Cursio JF, Hollenberg SM, Sutton-Tyrrell K, … Everson-Rose SA. Depressive symptoms are related to progression of coronary calcium in midlife women: The Study of Women's Health Across the Nation (SWAN) Heart Study. American Heart Journal. 2011; 161(6):1186–1191. [PubMed: 21641367]

Janssen I, Powell LH, Matthews KA, Jasielec MS, Hollenberg SM, Bromberger JT, … Everson-Rose SA. Relation of persistent depressive symptoms to coronary artery calcification in women aged 46 to 59 years. 2016; doi: 10.1016/j.amjcard.2016.03.035

Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, … Wang PS. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). The Journal of the American Medical Association. 2003; 289(23):3095–3105. [PubMed: 12813115]

Kondos GT, Hoff JA, Sevrukov A, Daviglus ML, Garside DB, Devries SS, … Liu K. Electron-beam tomography coronary artery calcium and cardiac events: A 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. Circulation. 2003; 107(20):2571–2576. DOI: 10.1161/01.CIR.0000068341.61180.55 [PubMed: 12743005]

Kruijshaar ME, Barendregt J, Vos T, de Graaf R, Spijker J, Andrews G. Lifetime prevalence estimates of major depression: An indirect estimation method and a quantification of recall bias. European Journal of Epidemiology. 2005; 20(1):103–111. [PubMed: 15756910]

Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, … Wulsin L. Depression as a risk factor for poor prognosis among patients with acute coronary syndrome: systematic review and recommendations: A scientific statement from the American Heart Association. Circulation. 2014; 129(12):1350–1369. [PubMed: 24566200]

Loria CM, Liu K, Lewis CE, Hulley SB, Sidney S, Schreiner PJ, … Detrano R. Early adult risk factor levels and subsequent coronary artery calcification - The CARDIA study. Journal of the American College of Cardiology. 2007; 49(20):2013–2020. DOI: 10.1016/j.jacc.2007.03.009 [PubMed: 17512357]

Lyons M, Hitsman B, Xian H, Panizzon MS, Jerskey BA, Santangelo S, … Tsuang MT. A twin study of smoking, nicotine dependence, and major depression in men. Nicotine and Tobacco Research. 2008; 10(1):97–108. DOI: 10.1080/14622200701705332 [PubMed: 18188750]

Matthews KA, Chang YF, Sutton-Tyrrell K, Edmundowicz D, Bromberger JT. Recurrent major depression predicts progression of coronary calcification in healthy women: Study of Women's Health Across the Nation. Psychosomatic Medicine. 2010; 72(8):742–747. DOI: 10.1097/PSY.0b013e3181eeeb17 [PubMed: 20668281]

Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: A glucocorticoid-resistance model. Health Psychology. 2002; 21(6):531–541. [PubMed: 12433005]

Mukamal KJ, Conigrave KM, Mittleman MA, Camargo CA Jr, Stampfer MJ, Willett WC, Rimm EB. Roles of drinking pattern and type of alcohol consumed in coronary heart disease in men. New England Journal of Medicine. 2003; 348(2):109–118. [PubMed: 12519921]

Munafo MR, Hitsman B, Rende R, Metcalfe C, Niaura R. Effects of progression to cigarette smoking on depressed mood in adolescents: Evidence from the National Longitudinal Study of Adolescent Health. Addiction. 2008; 103(1):162–171. [PubMed: 18031565]

Nicholson A, Kuper H, Hemingway H. Depression as an aetiologic and prognostic factor in coronary heart disease: A meta-analysis of 6362 events among 146 538 participants in 54 observational studies. European Heart Journal. 2006; 27(23):2763–2774. DOI: 10.1093/eurheartj/ehl338 [PubMed: 17082208]

O'Neil A, Fisher AJ, Kibbey KJ, Jacka FN, Kotowicz MA, Williams LJ, … Pasco JA. Depression is a risk factor for incident coronary heart disease in women: An 18-year longitudinal study. Journal of Affective Disorders. 2016; 196:117–124. DOI: 10.1016/j.jad.2016.02.029 [PubMed: 26921864]

Pletcher MJ, Varosy P, Kiefe CI, Lewis CE, Sidney S, Hulley SB. Alcohol consumption, binge drinking, and early coronary calcification: Findings from the Coronary Artery Risk Development in Young Adults (CARDIA) Study. American Journal of Epidemiology. 2005; 161(5):423–433. DOI: 10.1093/aje/kwi062 [PubMed: 15718478]

Pletcher MJ, Vittinghoff E, Kalhan R, et al. Association between marijuana exposure and pulmonary function over 20 years. The Journal of the American Medical Association. 2012; 307(2):173–181. DOI: 10.1001/jama.2011.1961 [PubMed: 22235088]

Poli A, Marangoni F, Avogaro A, Barba G, Bellentani S, Bucci M, … Visioli F. Moderate alcohol use and health: A consensus document. Nutrition, Metabolism and Cardiovascular Diseases. 2013; 23(6):487–504. DOI: 10.1016/j.numecd.2013.02.007

Pratt LA, Brody DJ. Depression and smoking in the U.S. household population aged 20 and over, 2005–2008. National Center for Health Statistics Data Brief. 2010; (34):1–8.

Radloff LS. The CES-D Scale: A self-report depression scale for research in the general population. Applied Psychological Measurement. 1977; 1(3):385–401. DOI: 10.1177/014662167700100306

Rasmussen T, Frestad D, Kober L, Pedersen JH, Thomsen LH, Dirksen A, Kofoed KF. Development and progression of coronary artery calcification in long-term smokers: Adverse effects of continued smoking. Journal of the American College of Cardiology. 2013; 62(3):255–257. DOI: 10.1016/j.jacc.2013.04.013 [PubMed: 23643591]

Reis JP, Loria CM, Lewis CE, Powell-Wiley TM, Wei GS, Carr JJ, … Liu K. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. Journal of the American Medical Association. 2013; 310(3):280–288. DOI: 10.1001/jama.2013.7833 [PubMed: 23860986]

Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. New England Journal of Medicine. 2000; 342(12):836–843. [PubMed: 10733371]

Schwarz, N. Retrospective and Concurrent Self-Reports: The Rationale for Real-Time Data Capture. In: Stone, AA.Shiffman, SS.Atienza, A., Nebeling, L., editors. The Science of Real-Time Data Capture: Self-reports in Health Research. New York: Oxford University Press; 2007.

Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. European Heart Journal. 2006; 27(8):968–975. DOI: 10.1093/eurheartj/ehi750 [PubMed: 16443606]

Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology. 2003; 228(3):826–833. DOI: 10.1148/radiol.2283021006 [PubMed: 12869688]

Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain, Behavior, and Immunity. 2009; 23(7):936–944.

Stewart JC, Zielke DJ, Hawkins MAW, Williams DR, Carnethon MR, Knox SS, Matthews KA. Depressive symptom clusters and 5-year incidence of coronary artery calcification: The Coronary Artery Risk Development in Young Adults Study. Circulation. 2012; 126(4):410–417. DOI: 10.1161/circulationaha.112.094946 [PubMed: 22711275]

Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: Systematic review and meta-analysis. British Medical Journal. 2014; 348doi: 10.1136/bmj.g1151

USDHHS. How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. Rockville, MD, Washington, DC: United States Department of Health and Human Services, Public Health Service; 2010.

USDHHS. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

van der Vaart H, Postma DS, Timens W, Ten Hacken NHT. Acute effects of cigarette smoke on inflammation and oxidative stress: A review. Thorax. 2004; 59(8):713–721. DOI: 10.1136/thx.2003.012468 [PubMed: 15282395]

Vittinghoff, E., Glidden, DV., Shiboski, CE., McCulloch, CE. Regression Methods in Biostatistics: Linear, Logistic, Survival, and Repeated Measures Models. 2. Springer; 2012. Missing Data; p. 431-468.

WHO. The top 10 causes of death. World Health Organization; 2013.

Yaffe K, Vittinghoff E, Pletcher MJ, Hoang TD, Launer LJ, Whitmer R, … Sidney S. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation. 2014; 129(15):1560–1567. DOI: 10.1161/circulationaha.113.004798 [PubMed: 24687777]

Yan LL, Liu K, Daviglus ML, Colangelo LA, Kiefe CI, Sidney S, … Greenland P. Education, 15-year risk factor progression, and coronary artery calcium in young adulthood and early middle age: The Coronary Artery Risk Development in Young Adults study. The Journal of the American Medical Association. 2006; 295(15):1793–1800. DOI: 10.1001/jama.295.15.1793 [PubMed: 16622141]

Young-Wolff KC, Kendler KS, Sintov ND, Prescott CA. Mood-related drinking motives mediate the familial association between major depression and alcohol dependence. Alcoholism, Clinical and Experimental Research. 2009; 33(8):1476–1486. DOI: 10.1111/j.1530-0277.2009.00978.x

**Table 1**

Participant characteristics by level of CAC at Year 25.

| | | Level of CAC | | | |
|---|---|---|---|---|---|
| **Variable** | **All participants (N=3,189)** | **CAC=0 (n=2,282)** | **CAC=1-99 (n=597)** | **CAC ≥100 (n=310)** | ***p*-value** |
| *Gender x Race* | | | | | <.001 |
| Black women, n (%) | 915 (29%) | 743 (33%) | 121 (20%) | 51 (16%) | |
| Black men, n (%) | 602 (19%) | 391 (17%) | 130 (22%) | 81 (26%) | |
| White women, n (%) | 890 (28%) | 740 (32%) | 108 (18%) | 42 (14%) | |
| White men, n (%) | 782 (25%) | 408 (18%) | 238 (40%) | 136 (44%) | |
| Age (years), mean (SD) | 50.1 (3.6) | 49.7 (3.7) | 50.8 (3.3) | 52.1 (3.0) | <.001 |
| Education (years), median (IQR) | 16 (3) | 16 (4) | 16 (3) | 15 (3) | <.001 |
| Cholesterol (mg/dL), median (IQR) | 181.7 (33.9) | 179.1 (32.6) | 188.4 (34.0) | 191.4 (35.0) | <.001 |
| SBP (mmHg), median (IQR) | 111.3 (12.6) | 109.8 (12.3) | 113.4 (12.1) | 116.8 (12.7) | <.001 |
| DBP (mmHg), median (IQR) | 71.0 (8.9) | 70.3 (8.9) | 72.0 (9.4) | 74.6 (7.8) | <.001 |
| BMI ($kg/m^2$), median (IQR) | 26.2 (6.7) | 25.8 (6.6) | 26.7 (6.7) | 27.3 (6.8) | .017 |
| Diabetes, n (%) | 437 (14%) | 264 (12%) | 103 (17%) | 70 (23%) | <.001 |
| Physical activity score, median (IQR) | 5.7 (1.0) | 5.7 (1.0) | 5.8 (0.9) | 5.8 (1.0) | .007 |
| Alcohol use[a] (drinkyears) | 17.4 (25.5) | 15.8 (23.6) | 19.1 (25.4) | 27.2 (39.9) | <.001 |
| *Cigarette smoking* | | | | | |
| Smoking[b] (packyears), median (IQR) | 7.1 (15.5) | 5.9 (13.4) | 10.4 (19.6) | 13.7 (19.1) | <.001 |
| Year 25 cigarettes/day[c], M (SD) | 11.1 (7.9) | 10.2 (6.9) | 13.5 (9.7) | 10.9 (7.7) | .003 |
| *Depressive symptoms* | | | | | |
| CES-D score, median[d] (IQR) | 8.7 (7.6) | 8.7 (7.5) | 8.6 (7.4) | 9.6 (9.5) | .085 |
| Year 25 CES-D score, mean (SD) | 7.8 (9.5) | 9.5 (7.8) | 9.3 (7.4) | 10.1 (7.9) | .394 |

Values for the following variables are the TWA-AUC estimates: total cholesterol, SBP, DBP, BMI, physical activity score, alcohol use, smoking, and CES-D score. These values are presented as median (IQR).

[a] Mean drinkyears among ever drinkers, N=1,751 (CAC=0: n=1,217, CAC 1-99: n=352, CAC ≥100: n=182).

[b] Mean packyears among ever smokers, N=1,576 (CAC=0: n=1,059, CAC 1-99: n=319, CAC ≥100: n=201).

[c] Mean cigarettes/day among Year 25 smokers, N=568 (CAC=0: n=337, CAC 1-99: n=129, CAC ≥100: n=102).

[d] TWA-AUC CES-D score: N=3,188 (CAC=0: n=2,281, CAC 1-99: n=597, CAC ≥100: n=310).

Abbreviations: CAC, coronary artery calcification; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CES-D, Center for epidemiologic studies – Depression scale; SD: standard deviation; IQR: interquartile range; TWA: time-weighted average; AUC: area under the curve.

## Table 2

Full model results for multinomial regression analysis evaluating the association between the interaction of cumulative smoking and cumulative depressive symptoms over 25 years with CAC at Year 25 (N=3,188)

| | CAC=0 vs. CAC 1-99 | | CAC=0 vs. CAC ≥100 | |
|---|---|---|---|---|
| **Variable** | **OR (95% CI)** | ***p*-value** | **OR (95% CI)** | ***p*-value** |
| Gender x Race [a] | | | | |
| Black women | 0.90 (0.66–1.25) | .538 | 0.62 (0.38–1.02) | .058 |
| Black men | **1.81 (1.29–2.53)** | **.001** | **1.99 (1.25–3.17)** | **.004** |
| White men | **3.45 (2.58–4.60)** | **<.001** | **4.07 (2.68–6.18)** | **<.001** |
| Age (1 year) | **1.09 (1.06–1.13)** | **<.001** | **1.26 (1.20–1.31)** | **<.001** |
| Education (1 year) | 0.98 (0.94–1.02) | .299 | 0.95 (0.90–1.01) | .097 |
| Total cholesterol (0.1 mg/dL) | **1.14 (1.10–1.19)** | **<.001** | **1.22 (1.16–1.28)** | **<.001** |
| SBP (10 mmHg) | **1.28 (1.05–1.56)** | **.015** | **1.97 (1.53–2.55)** | **<.001** |
| DBP (10 mmHg) | 0.99 (0.77–1.29) | .967 | 0.90 (0.64–1.27) | .548 |
| BMI (5 kg/m$^2$) | **1.20 (1.09–1.33)** | **<.001** | **1.25 (1.09–1.44)** | **.001** |
| Diabetes status | 1.31 (0.99–1.73) | .063 | 1.43 (0.99–2.05) | .054 |
| Physical activity | 1.13 (0.98–1.30) | .084 | 1.04 (0.86–1.24) | .705 |
| Alcohol use [b] | | .316 | | .372 |
| 8 drinkyears | 1.02 (0.91–1.15) | .730 | 1.10 (0.94–1.29) | .232 |
| 30 drinkyears | 1.01 (0.77–1.33) | .952 | 1.28 (0.88–1.87) | .197 |
| Smoking (10 packyears) [c] | **1.35 (1.22–1.49)** | **<.001** | **1.46 (1.29–1.66)** | **<.001** |
| Depressive symptoms [d] (16 CES-D points) | 0.78 (0.57–1.07) | .121 | 1.00 (0.66–1.51) | .985 |
| Smoking x depressive symptoms [e] | | **.036** | | **.001** |

[a]White women is the reference category.

[b]Alcohol use: 0 drinkyears is the reference category.

[c]Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25.

[d]Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Year 5, 10, 15, 20, and 25.

[e]To facilitate interpretation of the interaction, please see Tables 3a (CAC 1-99) and 3b (CAC ≥100).

**Bold** indicates $p<.05$. Presented values for the following variables are TWA-AUC estimates: total cholesterol, SBP, DBP, BMI, physical activity, alcohol use, smoking, and depressive symptoms. Abbreviations: CAC, coronary artery calcification; OR, Odds Ratio; 95% CI, 95% Confidence Interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

## Table 3a

Odds Ratio (95% Confidence Interval) of moderate-risk CAC (Agatston score 1-99) at Year 25 by cumulative smoking x depressive symptoms over 25 years

| | Depressive symptoms (TWA-AUC of CES-D) | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | 0.97 (0.93–1.01) | 0.86 (0.70–1.04) | 0.78 (0.57–1.06) |
| 10 | **1.35 (1.22–1.49)** | **1.34 (1.12–1.61)** | **1.34 (1.02–1.75)** |
| 20 | **1.87 (1.53–2.29)** | **2.10 (1.60–2.75)** | **2.29 (1.57–3.34)** |
| 30 | **2.60 (1.93–3.50)** | **3.28 (2.20–4.90)** | **3.91 (2.25–6.81)** |

**Bold** indicates a significant ($p$<.05) association between the smoking by depressive symptoms interaction with odds of CAC 1-99 (3a) or CAC ≥100 (3b) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

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**Table 3b**

Odds Ratio (95% Confidence Interval) of higher-risk CAC (Agatston score ≥100) at Year 25 by cumulative smoking x depressive symptoms over 25 years

| | **Depressive symptoms (TWA-AUC of CES-D)** | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | 1.00 (0.95–1.05) | 1.00 (0.77–1.29) | 1.00 (0.66–1.51) |
| 10 | **1.50 (1.32–1.71)** | **1.69 (1.33–2.14)** | **1.84 (1.29–2.62)** |
| 20 | **2.26 (1.77–2.89)** | **2.85 (2.06–3.95)** | **3.39 (2.16–5.32)** |
| 30 | **3.40 (2.36–4.90)** | **4.82 (3.03–7.66)** | **6.25 (3.31–11.83)** |

**Bold** indicates a significant ($p$<.05) association between the smoking by depressive symptoms interaction with odds of CAC 1-99 (3a) or CAC ≥100 (3b) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

## Table 4

Full model results for multinomial regression analysis evaluating the association between the interaction of cumulative smoking and cumulative depressive symptoms over 25 years with CAC at Year 25, and adjusted for the alcohol use x depressive symptoms interaction (N=3,188)

| | CAC=0 vs. CAC 1-99 | | CAC=0 vs. CAC ≥100 | |
|---|---|---|---|---|
| **Variable** | **OR (95% CI)** | ***p*-value** | **OR (95% CI)** | ***p*-value** |
| Gender x Race [a] | | | | |
| Black women | 0.93 (0.67–1.28) | .642 | 0.63 (0.38–1.03) | .065 |
| Black men | **1.84 (1.32–2.58)** | **<.001** | **2.04 (1.27–3.25)** | **.003** |
| White men | **3.46 (2.60–4.63)** | **<.001** | **4.10 (2.70–6.24)** | **<.001** |
| Age (1 year) | **1.10 (1.07–1.13)** | **<.001** | **1.25 (1.20–1.31)** | **<.001** |
| Education (1 year) | 0.98 (0.94–1.02) | .309 | 0.95 (0.90–1.01) | .096 |
| Total cholesterol (0.1 mg/dL) | **1.14 (1.10–1.19)** | **<.001** | **1.22 (1.16–1.28)** | **<.001** |
| SBP (10 mmHg) | **1.29 (1.06–1.57)** | **.011** | **1.97 (1.52–2.54)** | **<.001** |
| DBP (10 mmHg) | 0.98 (0.76–1.28) | .908 | 0.91 (0.64–1.29) | .590 |
| BMI (5 kg/m$^2$) | **1.20 (1.09–1.33)** | **<.001** | **1.24 (1.09–1.43)** | **.002** |
| Diabetes status | 1.29 (0.97–1.71) | .082 | 1.41 (0.98–2.02) | .064 |
| Physical activity | 1.13 (0.98–1.29) | .093 | 1.04 (0.86–1.24) | .705 |
| Alcohol use[b] | | .065 | | .342 |
| 8 drinkyears | 1.04 (0.92–1.18) | .482 | 1.10 (0.93–1.29) | .271 |
| 30 drinkyears | 1.03 (0.78–1.36) | .835 | 1.27 (0.87–1.86) | .216 |
| Smoking (10 packyears)[c] | **1.36 (1.22–1.50)** | **<.001** | **1.46 (1.29–1.66)** | **<.001** |
| Depressive symptoms[d] (16 CES-D points) | 0.89 (0.59–1.34) | .580 | 1.26 (0.73–2.19) | .400 |
| Smoking x depressive symptoms[e] | | .056 | | **.001** |
| Alcohol use x depressive symptoms | | **.048** | | .379 |
| 8 drinkyears | 0.80 (0.60–1.07) | .130 | 0.82 (0.56–1.18) | .279 |
| 30 drinkyears | 0.66 (0.34–1.30) | .232 | 0.59 (0.25–1.38) | .227 |

[a]White women is the reference category.

[b]Alcohol use: 0 drinkyears is the reference category.

[c]Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25.

[d]Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Year 5, 10, 15, 20, and 25.

[e]To facilitate interpretation of the interaction, please see Tables 5a through 5d.

**Bold** indicates $p$<.05. Presented values for the following variables are TWA-AUC estimates: total cholesterol, SBP, DBP, BMI, physical activity, alcohol use, smoking, and depressive symptoms. Abbreviations: CAC, coronary artery calcification; OR, Odds Ratio; 95% CI, 95% Confidence Interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

## Table 5a

Odds Ratio (95% Confidence Interval) of moderate-risk CAC (Agatston score 1-99) at Year 25 by cumulative smoking x depressive symptoms over 25 years at no alcohol use (0 drinkyears)

| | Depressive symptoms (TWA-AUC of CES-D) | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | 0.99 (0.94–1.04) | 0.93 (0.72–1.20) | 0.89 (0.59–1.34) |
| 10 | **1.38 (1.23–1.54)** | **1.45 (1.10–1.90)** | 1.51 (0.99–2.30) |
| 20 | **1.92 (1.56–2.36)** | **2.26 (1.57–3.24)** | **2.56 (1.49–4.38)** |
| 30 | **2.68 (1.97–3.63)** | **3.52 (2.17–5.74)** | **4.33 (2.13–8.83)** |

**Bold** indicates a significantly (*p*<.05) greater odds of CAC 1-99 (5a and 5b) or CAC ≥100 (5c and 5d) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. The model was run centered on drinkyears=0 (5a and 5c) and drinkyears=8 (i.e., median alcohol use; 5b and 5d). Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; 1 is ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

### Table 5b

Odds Ratio (95% Confidence Interval) of moderate-risk CAC (Agatston score 1-99) at Year 25 by cumulative smoking x depressive symptoms over 25 years at median alcohol use (8 drinkyears)

| | Depressive symptoms (TWA-AUC of CES-D) | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | **0.96 (0.92–1.00)** | **0.80 (0.66–0.98)** | **0.70 (0.51–0.97)** |
| 10 | **1.34 (1.20–1.48)** | **1.25 (1.03–1.52)** | 1.19 (0.89–1.60) |
| 20 | **1.86 (1.52–2.28)** | **1.95 (1.46–2.62)** | **2.02 (1.33–3.07)** |
| 30 | **2.60 (1.93–3.51)** | **3.04 (1.99–4.66)** | **3.43 (1.87–6.28)** |

**Bold** indicates a significantly ($p$<.05) greater odds of CAC 1-99 (5a and 5b) or CAC ≥100 (5c and 5d) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. The model was run centered on drinkyears=0 (5a and 5c) and drinkyears=8 (i.e., median alcohol use; 5b and 5d). Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; 1 is ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

## Table 5c

Odds Ratio (95% Confidence Interval) of higher-risk CAC (Agatston score ≥100) at Year 25 by cumulative smoking x depressive symptoms over 25 years at no alcohol use (0 drinkyears)

| | **Depressive symptoms (TWA-AUC of CES-D)** | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | 1.03 (0.96–1.10) | 1.16 (0.82–1.63) | 1.26 (0.73–2.19) |
| 10 | **1.56 (1.36–1.79)** | **2.01 (1.42–2.86)** | **2.44 (1.42–4.20)** |
| 20 | **2.36 (1.83–3.03)** | **3.50 (2.26–5.43)** | **4.72 (2.46–9.05)** |
| 30 | **3.57 (2.47–5.17)** | **6.10 (3.45–10.77)** | **9.10 (3.97–20.88)** |

**Bold** indicates a significantly ($p$<.05) greater odds of CAC 1-99 (5a and 5b) or CAC ≥100 (5c and 5d) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. The model was run centered on drinkyears=0 (5a and 5c) and drinkyears=8 (i.e., median alcohol use; 5b and 5d). Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; 1 is ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.

**Table 5d**

Odds Ratio (95% Confidence Interval) of higher-risk CAC (Agatston score ≥100) at Year 25 by cumulative smoking x depressive symptoms over 25 years at median alcohol use (8 drinkyears)

| | **Depressive symptoms (TWA-AUC of CES-D)** | | |
|---|---|---|---|
| **Smoking (Packyears)** | **2** | **10** | **16** |
| 0 | 1.00 (0.78–1.33) | 1.02 (0.78–1.33) | 1.03 (0.67–1.57) |
| 10 | **1.52 (1.33–1.73)** | **1.77 (1.37–2.28)** | **1.98 (1.35–2.91)** |
| 20 | **2.30 (1.80–2.94)** | **3.07 (2.16–4.37)** | **3.82 (2.32–6.30)** |
| 30 | **3.48 (2.41–5.02)** | **5.35 (3.26–8.77)** | **7.38 (3.69–14.79)** |

**Bold** indicates a significantly (*p*<.05) greater odds of CAC 1-99 (5a and 5b) or CAC ≥100 (5c and 5d) relative to CAC =0, smoking exposure =0 packyears, and depressive symptoms (TWA-AUC of CES-D) =0. The model was run centered on drinkyears=0 (5a and 5c) and drinkyears=8 (i.e., median alcohol use; 5b and 5d). Smoking (packyears) was a cumulative measure of cigarette packyears assessed annually from Year 0 through Year 25. Depressive symptoms (CES-D score) was a TWA-AUC of cumulative CES-D scores assessed at Years 5, 10, 15, 20, and 25. Possible range for CES-D scores: 0–60; 1 is ≥10 is the threshold over which approximately 20% of the sample fell; ≥16 is used as a standard cutoff for clinically elevated depressive symptoms (Radloff, 1977). Abbreviations: CAC, coronary artery calcification; CES-D, Center for epidemiologic studies Depression scale; TWA: time-weighted average; AUC: area under the curve.