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Evaluating longitudinal associations between depressive symptoms, smoking, and biomarkers of cardiovascular disease in the CARDIA study

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Abstract

Objective: To evaluate associations between 15-year trajectories of co-occurring depressive symptoms and smoking with biomarkers of cardiovascular disease at Year 15.

Methods: In the Coronary Artery Risk Development in Young Adults (CARDIA) study, we modeled trajectories of depressive symptoms (Center for Epidemiologic Studies – Depression scale: CES-D) and smoking (cigarettes per day: CPD) among 3,614 adults followed from Year 0 (ages 18–30) through Year 15 (ages 33–45). Biomarkers of inflammation (hsCRP), oxidative stress (SOD, F2-isoprostanes), and endothelial dysfunction (sICAM1, sP-selectin) were assessed at Year 15. We conducted separate linear regression analyses with CES-D trajectory, CPD trajectory, and their interaction with each of the five biomarkers.

Results: The sample was 56% women, 47% Black, and 40 years old on average at Year 15. The CES-D trajectory x CPD trajectory interaction was not associated with any of the biomarkers (all $p>.01$). Removing the interaction term, CES-D trajectory was associated with inflammation: higher levels of hsCRP were observed in the subthreshold ($\beta=0.57$, $p=.004$) and increasing depressive symptoms ($\beta=1.36$, $p<.001$) trajectories compared to the no depression trajectory. CPD trajectory was associated with oxidative stress and endothelial dysfunction: compared to never smokers, heavy smokers had significantly higher levels of F2-isoprostanes ($\beta=6.20$, $p=.001$), sICAM1 ($\beta=24.98$, $p<.001$), and sP-selectin ($\beta=2.91$, $p<.001$).

Conclusions: Co-occurring depressive symptoms and smoking do not appear to synergistically convey risk for cardiovascular disease via processes of inflammation, oxidative stress, or endothelial dysfunction. Nonetheless, these results advance our understanding of the complex relationships between modifiable risk factors and chronic disease.

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Keywords

depression; smoking; inflammation; oxidative stress; endothelial dysfunction; cardiovascular disease

Among otherwise healthy adults, depression independently places individuals at increased risk of developing cardiovascular disease (CVD) (1, 2). Despite the growth of research in this area, the underlying mechanisms by which depression negatively impacts cardiovascular health remains unclear. Several physiological processes have been identified as potential mechanisms, including inflammation, oxidative stress, and endothelial dysfunction (3–6).

Inflammation, or the presence of inflammatory markers, is perhaps the most studied of these processes (7). Consistently, cross-sectional studies have shown that adults with elevated depressive symptoms have higher levels of pro-inflammatory markers, including high-sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6), interleukin receptor antagonist, and white blood cell count (8–11). Longitudinally, Stewart, et al. (12) observed that depression preceded and augmented IL-6 levels over 6 years, while others found that hsCRP levels, but not IL-6, were predicted by persistent depressive symptoms over 6 months (13). Some have shown that hsCRP levels decrease after treatment with antidepressant medication (specifically, selective serotonin reuptake inhibitors; SSRIs), even when depressive symptoms did not improve (14, 15).

Likewise, findings from systematic reviews and meta-analyses examining the association between depression and oxidative stress found higher levels of superoxide dismutase (SOD), F2-isoprostanes, and 8-hydroxy-2'-deoxyguanosine (8-OHdG) and lower levels of antioxidants among adults with elevated depressive symptoms or major depressive disorder (16–18). Others found that depressive symptoms among women were independently associated with higher levels of 8-OHdG (19). One meta-analysis also concluded that antidepressant treatment was associated with lower levels of oxidative stress markers (17).

For endothelial dysfunction, a number of studies in both healthy and medical populations have demonstrated associations of elevated depressive symptoms or major depressive disorder and endothelial dysfunction as assessed by flow-mediated dilation (20–22) and sP-selectin (23, 24). In contrast with markers of inflammation or oxidative stress, endothelial function as assessed by flow-mediated dilation remains impaired even in treated depression (25), although one study demonstrated reductions in sP-selection following treatment with an SSRI (24). Few studies have evaluated an association between depression and cell adhesion molecules (CAMs; e.g., sICAM1). However, one cross-sectional study found a positive association between depressive symptoms and sICAM1 concentrations among elderly diabetic patients with mild cognitive impairment (26).

The association between depression and these processes is likely further complicated by behavioral factors known to negatively impact cardiovascular health, such as smoking. In a previous study, we found that cumulative exposure to both depressive symptoms and cigarette smoking was synergistically associated with even higher odds of coronary artery calcification, an important marker of CVD risk, among middle-aged adults (27). Therefore,

it is important to evaluate the associations between depressive symptoms and these biomarkers of physiological processes by which depression is hypothesized to contribute to development of CVD within the context of smoking patterns.

In most cases, previous studies that have found associations between elevated depressive symptoms and higher levels of biomarkers of inflammation, oxidative stress, and endothelial dysfunction adjusted for smoking status, but none have examined the interactive effects of depressive symptoms and smoking on these biomarkers. Moreover, few studies have evaluated multiple biomarkers within the same sample to compare associations between depressive symptoms and smoking with different physiological processes of CVD. Finally, our current understanding of the mechanisms underlying the negative impact of depression on CVD comes primarily from studies of depression in patients with preexisting CVD, while few studies have evaluated prospective associations between depressive symptoms and biomarkers of CVD among young, healthy adults.

The present study aimed to address these gaps by evaluating associations between patterns of depressive symptoms and smoking throughout young adulthood with subsequent levels of biomarkers of physiological processes by which depression is hypothesized to contribute to development of CVD. Using data from the Coronary Artery Risk Development in Young Adults (CARDIA) study, we tested whether the interaction between patterns of depressive symptoms and patterns of smoking over 15 years is associated with biomarkers of inflammation, oxidative stress, endothelial dysfunction, or a combination thereof. Specifically, we hypothesized that participants with patterns of high or increasing exposure to depressive symptoms and smoking would have synergistically higher levels of hsCRP, SOD, F2-isoprostanes, sP-selectin, and sICAM1 relative to participants with patterns of high or increasing exposure to depressive symptoms alone, smoking alone, or neither.

Methods

Study description

The CARDIA Study (<http://www.cardia.dopm.uab.edu/>) is an ongoing longitudinal, community-based cohort study sponsored by the National Heart, Lung, and Blood Institute in which 5,115 young adults were recruited in 1985 and have been followed for 30 years. This study was a secondary analysis using data from Year 0 (March 1985-June 1986) through Year 15 (May 2000-June 2001), when all the biomarkers were collected on the majority of the study sample. The present analyses were limited to those participants who had data for at least one biomarker. All procedures were IRB approved at each of the study sites, and informed consent was completed by each participant at each exam.

Participants

The CARDIA sample comprises adults aged 18–30 years in 1985–1986 who were recruited from four field centers in the United States. Recruitment was stratified on baseline sex, race (Black and White), age (18–24 years and 25–30 years), education (high school graduate and > high school graduate), and study site (Birmingham, Alabama; Minneapolis, Minnesota; Chicago, Illinois; and Oakland, California). Follow-up in-person exams were

completed at Year 2, 5, 7, 10, 15, 20, 25, and 30, with annual telephone contacts between in-person exams.

Measures

Depressive symptoms.—The Center for Epidemiologic Studies Depression (CES-D) scale (28) assesses 20 symptoms on a scale from 0 (never) to 3 (nearly every day), with scores ranging from 0 (none/low depressive symptoms) to 60 (high depressive symptoms), where scores ≥ 16 are considered to be clinically significant. The CES-D was administered to participants at Years 5 ($\alpha=0.88$), 10 ($\alpha=0.89$), and 15 ($\alpha=0.89$).

Smoking.—At each exam (Years 0, 2, 5, 7, 10, and 15) participants were asked if they were currently smoking (at least 5 cigarettes per week). If participants were current smokers, they were asked about the average number of cigarettes per day (CPD) that they were currently smoking; non-smokers or former smokers were recorded as smoking 0 CPD.

Biomarkers.—All biomarkers were assessed at Year 15. *Inflammation* was measured by high-sensitivity C-reactive protein (hsCRP; coefficient of variation: CV=166.3%). *Oxidative stress* was measured by superoxide dismutase (SOD; CV=47.3%) and F2-isoprostanes (CV=54.7%). *Endothelial dysfunction* was measured by cell adhesion molecules, specifically soluble P-selectin (sP-selectin; CV=30.5%) and soluble intercellular adhesion molecule-1 (sICAM1; CV=29.0%).

Detailed collection and measurement procedures are detailed elsewhere (29). Briefly, participants were asked to fast for at least 8 hours and avoid smoking and heavy physical activity for at least 2 hours prior to their appointment. Whole blood samples were collected and plasma or serum aliquots were stored at -70°C until processed. Serum hsCRP was assessed by ELISA, SOD activity was measured by following kit procedures, sP-selectin and sICAM1 immunoassays were assessed by ELISA, and F2-isoprostanes were assessed by gas chromatography-mass spectrometry.

Data analysis

All analyses were conducted using SAS, Version 9.4 (Cary, NC).

Trajectory modeling.—We modeled trajectories of CES-D scores and CPD using *proc traj* (30, 31). CES-D score trajectories used data from Years 5, 10, and 15 using the censored normal (CNORM) model. CPD trajectories used data from Years 0, 2, 5, 7, 10, and 15 using the zero-inflated Poisson (ZIP) model due to the large proportion of 0-values (i.e., nonsmokers). We first ran each model with a cubic function; however, given the limited availability of data for CES-D scores through Year 15, we assigned lower polynomial function (linear) to reach a global maximum. Next, because trajectory models often find only the local maximum when using default start values, we ran each model using the recommended start parameters and polynomial function for each trajectory group to achieve a model that reached a global maximum (i.e., best-fit polynomial function for each trajectory group within the model) (31). We analyzed trajectory models with 2 through 10 groups, and model fit was assessed using the Bayesian Information Criterion (BIC). The optimal number

of trajectory groups was determined to be when the BIC was maximized or when adding more groups did not improve the BIC by >100 . The posterior predictive probability of group membership was calculated for each model, and participants were assigned to the trajectory group for which they had the greatest posterior predictive probability. We then qualitatively assessed the trajectory patterns and determined whether the patterns were clinically meaningful and named each trajectory group based on the observed patterns.

Missing data.—All participants who provided a blood sample for the biomarkers at the Year 15 CARDIA assessment were included; no missing data were imputed. Of the participants who attended the Year 15 visit ($n=3,671$), 3,614 participants (98.4%) had at least one biomarker measure, including 3,612 (98.4% of Year 15 sample) with CRP, 2,928 (79.8%) with SOD, 3,002 (81.8%) with F2-isoprostanes, 2,974 (81.0%) with sP-selectin, and 2,938 (80.0%) with sICAM1. Out of these 3,614 participants, 240 (6.5%) were missing Year 5 CES-D scores; 320 (8.8%) were missing Year 10 CES-D scores; and 43 (1.2%) were missing Year 15 scores. For CPD, 19 (0.5%), 158 (4.3%), 217 (6.0%), 287 (7.9%), 281 (7.8%), and 3 ($<0.01\%$) were missing CPD at Years 0, 2, 5, 7, 10, and 15, respectively. Trajectory modeling allows all participants with at least one measure of CES-D or CPD to be categorized into one of the respective trajectory groups. Therefore, none of the participants with available biomarker data were excluded from analysis due to missing CES-D or CPD data. Likewise, because the covariates included in all models (i.e., sex, race, age, and education) were collected at baseline, none of these data were missing.

Primary analyses.—We first evaluated Pearson correlations among Year 15 CES-D scores and CPD with each of the biomarkers. Separate linear regression analyses were then conducted to evaluate the association of CES-D trajectory, CPD trajectory, and CES-D trajectory $\times$ CPD trajectory interaction through Year 15 with each of the biomarkers (hsCRP, SOD, F2-isoprostanes, sP-selectin, sICAM1) at Year 15. For models with non-significant interaction terms, the interaction term was removed to evaluate the associations between the main effects of CES-D trajectory and CPD trajectory with the biomarkers. All models were adjusted for sociodemographic covariates (sex, race, age, and education), determined *a priori* (32). The reference categories were those trajectory patterns with the lowest exposure level (i.e., low CES-D scores and low CPD). The resulting least squares means were evaluated by trajectory group. To adjust for multiple testing of outcomes, a two-tailed p -value of $<.01$ (i.e., $p=.05/5$) was used to determine statistical significance.

Results

Descriptive results

At Year 15, 3,614 participants had data on at least one of the biomarkers and were included in the present analyses; sociodemographic, depressive symptoms, smoking, and biomarkers data for the sample at Year 15 are presented in Table 1. CES-D scores at Year 15 had small but significant, positive correlations with three out of five biomarkers. Higher levels of depressive symptoms were associated with modestly higher levels of hsCRP ($r=0.08$, $p<.001$), F2-Isoprostanes ($r=.06$, $p<.001$), and sICAM1 ($r=0.13$, $p<.001$), but not with SOD ($r=-0.01$, $p=.47$) or sP-selectin ($r=0.03$, $p=.084$). Likewise, higher CPD at Year 15 was

positively correlated with higher levels of hsCRP ($r=0.04$, $p=.007$), F2-Isoprostanes ($r=0.07$, $p<.001$), sP-selectin ($r=0.16$, $p<.001$), and sICAM1 ($r=0.34$, $p<.001$), but not with SOD ($r=0.00$, $p=.80$).

Trajectory models

The final trajectory models are presented in Figure 1. The CES-D model (Figure 1a) had 5 trajectories, characterized by low scores (“no depressive symptoms,” 55%), moderate, persistent scores <16 (“subthreshold depressive symptoms,” 33%), initially high scores that decreased to subthreshold levels (“decreasing depressive symptoms,” 4%), initially subthreshold scores that increased (“increasing depressive symptoms,” 7%), and persistently high scores (“high depressive symptoms,” 1%). The optimal CPD model (Figure 1b) had 5 trajectories, characterized by 0 CPD (“nonsmokers,” 52%), initial light smoking that decreased by Year 5 (“quitters,” 9%), persistent light smoking at 5 CPD (“light smokers,” 11%), persistent smoking that decreased over time from 10–15 CPD to 5–10 CPD (“moderate smokers,” 16%), and persistent smoking that decreased from 20–25 CPD to 10–15 CPD (“heavy smokers,” 12%).

Linear regression models evaluating the associations between CES-D trajectory, CPD trajectory, and both with Year 15 biomarkers

The CES-D trajectory x CPD trajectory interaction was not significant for any of the biomarkers at Year 15 after adjusting for multiple comparisons (hsCRP $p=.037$; SOD $p>.99$; F2-isoprostanes $p=.92$; sP-selectin $p=.92$; sICAM1 $p=.014$). However, there were main effects of CES-D trajectory and CPD trajectory for the different biomarkers. The least squares mean (standard error) results of the biomarkers by CES-D trajectory and by CPD trajectory for each of the main effects models are presented in Table 2.

For inflammation, CES-D trajectory was associated with hsCRP at Year 15 ($p<.001$), but CPD trajectory was not associated with hsCRP ($p=0.45$). Specifically, compared to hsCRP levels among the no depressive symptoms trajectory, significantly higher levels were observed among the subthreshold depressive symptoms trajectory ($\beta=0.57$, $p=0.004$) and the increasing depressive symptoms trajectory ($\beta=1.36$, $p<.001$) relative to the no depressive symptoms trajectory. High-sensitivity CRP levels were not significantly higher in the decreasing depressive symptoms trajectory ($\beta=0.09$, $p=0.87$) nor in the high depressive symptoms trajectory ($\beta=0.33$, $p=.67$).

For oxidative stress, the CPD trajectory were associated with F2-isoprostanes ($p=.002$). CES-D trajectory was not associated with F2-isoprostanes ($p=0.22$), and neither trajectory main effect was associated with SOD (CES-D trajectory $p=0.59$; CPD trajectory $p=0.55$). The main effect of CPD trajectory with F2-isoprostanes was driven by the difference in F2-isoprostane levels between the nonsmokers trajectory and both the moderate smokers trajectory ($\beta=4.75$, $p=0.007$) and the heavy smokers trajectory ($\beta=6.20$, $p=.001$); F2-isoprostanes levels did not differ significantly between the nonsmokers and the quitters ($\beta=-1.38$, $p=0.49$) nor the light smokers ($\beta=2.13$, $p=0.28$).

For endothelial dysfunction, CPD trajectory was associated with both sICAM1 ($p<.001$) and sP-selectin ($p<.001$). The association between CPD trajectory and sP-selectin was driven

only by the heavy smokers trajectory compared to the nonsmokers trajectory ($\beta=2.91$, $p<.001$). For sICAM1, all trajectories of persistent smoking were associated with higher levels of sICAM1 relative to the nonsmokers trajectory (light smokers $\beta=8.09$, $p=0.003$; moderate smokers $\beta=19.46$, $p<.001$; heavy smokers $\beta=24.98$, $p<.001$). CES-D trajectory was not associated with either sP-selection ($p=.21$) or sICAM1 ($p=0.028$) at Year 15.

Discussion

This study was, to our knowledge, the first to examine associations of longitudinal patterns of depressive symptoms and smoking with biomarkers of physiological processes by which depression and smoking may synergistically increase risk for CVD. In contrast with our hypothesis that there would be a synergistic association between patterns of high or increasing exposure to depressive symptoms and smoking with greater levels of inflammation, oxidative stress, or endothelial dysfunction biomarkers, we did not find depressive symptom trajectory by smoking trajectory interactions to be associated with any of the biomarkers at Year 15 after adjusting for multiple comparisons. However, we observed that depressive symptom patterns and smoking patterns were independently associated with different biomarkers.

First, we found an association between distinct patterns of depressive symptoms and inflammation. Specifically, individuals with a pattern of persistent, subthreshold depressive symptoms or a pattern of increasing depressive symptoms over 15 years had higher levels of hsCRP than those with consistently low levels of depressive symptoms. These findings are consistent with previous studies demonstrating positive correlations between depressive symptoms and inflammatory markers (33). It is also hypothesized that high levels of chronic, systemic inflammation predisposes individuals to depression (34, 35), suggesting a maintenance cycle between depressive symptoms and systemic inflammation that is likely moderated by other stress systems disruptions (e.g., the hypothalamic-pituitary-adrenal axis) (36). Ultimately, this confluence of symptoms and physiological disruptions may be responsible for the development of CVD that appears to stem directly and independently from chronically elevated depressive symptoms.

Of note, participants with the highest levels of depressive symptoms in the present sample did not have significantly higher levels of hsCRP. This could be because those participants with the highest levels of depressive symptoms were receiving antidepressant treatment, which has been shown to lower levels of inflammatory biomarkers even if depressive symptoms persist (14, 15), or it may be due to the small sample categorized in the highest depressive symptom trajectory and thus limited power to detect a statistically significant effect.

We did not observe an association between smoking patterns and inflammation (hsCRP). This finding may be related to the acute process by which cigarette smoking produces an inflammatory response (3), and is supported by other studies that did not find smoking heaviness to be associated with hsCRP levels (37). Notably, the mean hsCRP levels observed in our full sample were similar to those observed in other cohorts of middle-aged adults (38) and less than levels observed among smokers or persons with depressive disorders (37, 39).

Therefore, although a more sustained, systemic inflammatory state may be produced after many years of exposure to cigarettes, the participants in this study were relatively young and may not have built up the sustained inflammatory response.

The lack of an interaction between depressive symptoms and smoking with inflammation is surprising, given, for example, a cross-sectional study that found higher levels of inflammatory biomarkers among smokers with depression compared to smokers without depression (39). Our prospective results suggest that inflammatory processes may not be the mechanism by which elevated depressive symptoms and smoking exposure synergistically increase risk for CVD over time.

Second, we observed associations between smoking patterns and levels of F2-isoprostanes in a dose-dependent manner, as in previous studies (40). Patterns of depressive symptoms were not associated with either biomarker of oxidative stress in contrast with previous studies that found associations between a history of major depression and elevated F2-isoprostane levels (16, 17). In a cross-lagged panel analysis of CARDIA, both cross-sectional and longitudinal associations were observed between elevated depressive symptoms and F2-isoprostanes, but higher levels of F2-isoprostanes did not predict future elevations in depressive symptoms (41). The present study, to our knowledge the first to evaluate longitudinal patterns of depressive symptoms associated with oxidative stress, suggests that chronic exposure to elevated depressive symptoms is not associated with higher levels of oxidative stress in the future and it appears unlikely that oxidative stress is the primary mechanism by which depression increases risk for CVD.

Finally, we observed associations between smoking patterns, but not depressive symptom patterns, with both measures of endothelial dysfunction. The associations between patterns of smoking and endothelial dysfunction presented in a dose-dependent manner, where the trajectories of the highest exposure to cigarette smoking over 15 years had the largest levels of biomarkers of endothelial dysfunction. These associations were larger for sICAM1 compared to sP-selectin, where even participants at a mild level of smoking had higher levels of sICAM1 compared to nonsmokers. These findings are consistent with previous studies demonstrating a dose-dependent relationship between smoking and various measures of endothelial dysfunction (42, 43).

The lack of association between depressive symptom patterns and endothelial dysfunction levels contrasts with cross-sectional studies that found positive associations between depressive symptoms or depressed mood with greater endothelial dysfunction as measured by flow-mediated dilation (20, 21). Few studies have examined these relationships longitudinally. One study found correlations between depressive symptoms and endothelial dysfunction among adolescent to young adult females across multiple exams (44), while another found that older women with a history of major depressive disorder, but no current symptoms, had higher levels of endothelial dysfunction than women without a history of depression (45); taken together, these findings may be suggestive of residual elevations in endothelial dysfunction following a depressive episode. However, these studies comprised small sample sizes and in cross-sectional or retrospective designs. The present study

indicates that patterns of depressive symptoms may not be longitudinally or cumulatively associated with endothelial dysfunction, at least as it is measured by sICAM1 or sP-selectin.

It is debated whether any of these biomarkers are true mechanisms of initial CVD development despite the abundance of evidence demonstrating associations between biomarkers of inflammation, oxidative stress, or endothelial dysfunction and greater risk of poor outcomes or secondary events among adults with CVD (3). Even within the context of depression, some studies have found that these biomarkers explain only part of the association between depression and incident cardiovascular events. For example, adjusting for kidney function attenuated the mediating role of inflammatory markers between depressive symptoms and CVD (46). Most telling, studies implementing Mendelian randomization appear to refute a causal relationship between these biomarkers and incident CVD (7, 47, 48). However, a 2017 study found that administering a therapeutic dose of an anti-inflammatory therapy (150 mg of canakinumab every 3 months) to patients with CVD lowered their risk of a secondary nonfatal or nonfatal cardiovascular event by 15% compared to those administered a placebo (49). Nonetheless, some have argued that these biomarkers may be useful risk markers, rather than risk factors, for CVD, given that their associations with CVD are modest, at best, after accounting for traditional risk factors (7).

The presence of other psychological factors may further complicate the relationships between depression, smoking, and CVD. Anxiety, anger, and hostility traits have been associated with increased risk for CVD (50–52), and some have posited that rumination may be a mechanism by which depression increases risk for CVD (53). A hypothesis of general susceptibility to CVD due to mental disorders, particularly early in life, has also been proposed (54). This theory is supported by the results of the INTERHEART study, in which an index of psychosocial stress (including depression, stress, low locus of control, and major life events) was associated with more than 2.5 times greater odds of myocardial infarction per each additional stressor, even after accounting for other risk factors including smoking (55). Further studies are needed to delineate the complex relationships between biomarkers, behaviors, and psychological risk factors with CVD.

A major strength of this study was the variety of biomarkers, which allowed us to compare across and between physiological measures within a single sample. Furthermore, evaluating patterns of depressive symptoms and smoking over time allowed us to identify associations, and perhaps more importantly a lack thereof, that were not observed in cross-sectional analyses.

Nonetheless, there were some limitations. First, we cannot rule out multiple models producing false positives, although we adjusted for multiple testing and found cohesive patterns that met this more conservative threshold. Second, the results of the trajectory modeling that best fit the data only classified 1% of the sample in the high depressive symptoms group, which likely limited our power to detect a significant difference between that group and the no depression (reference) group. Third, as this was a secondary data analysis we were constrained by the available data, including: a single measurement of the biomarkers; non-quantified measures of antidepressant treatment or inflammatory diseases; or additional, latent factors that may contribute to these relationships, such as anxiety (which

is highly comorbid with depressive symptoms and implicated in CVD (51)) or estrogen levels (which are protective against CVD risk in pre-menopausal women (56)). For example, because hsCRP levels were not adjusted for inflammatory conditions, these results are likely somewhat overestimated. Fourth, selective attrition and/or mortality among smokers and among participants with elevated depressive symptoms may have attenuated our power to detect an interaction and also limits the generalizability of our results. Finally, although these physiological measures are hypothesized mechanisms by which psychological and behavioral factors increase risk for CVD, we did not evaluate any CVD endpoints (e.g., myocardial infarction) because of the young age and thus low event rate in the sample.

Conclusions

This study was the first to examine longitudinal patterns of depressive symptoms and smoking predicting biomarkers of physiological processes by which psychological and behavioral factors may increase risk for CVD. We did not find evidence supporting inflammation, endothelial dysfunction, or oxidative stress as physiological mechanisms by which depressive symptoms and smoking synergistically increase risk for CVD. Additional clinical, psychological, or behavioral mechanisms may contribute to our understanding of the risk of CVD attributable to depression, particularly within the context of co-occurring risk factors, such as smoking.

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Acronyms:

8-OHdG	8-hydroxy-2'-deoxyguanosine
CAM	cell adhesion molecules
CARDIA	Coronary Artery Risk Development in Young Adults study
CES-D	Center for Epidemiologic Studies – Depression scale
CPD	Cigarettes per day
CVD	cardiovascular disease
hsCRP	high-sensitivity C-reactive protein
IL-6	interleukin-6

sICAM1	soluble intercellular adhesion molecule-1
SOD	superoxide dismutase
sP-selectin	soluble <i>P</i> -selectin

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Figure 1.

a Trajectory model of depressive symptoms (Center for Epidemiologic Studies – Depression scale (CES-D) scores; N=4607): CARDIA, 1990–2001.

b Trajectory model of smoking (cigarettes per day (CPD); N=5112): CARDIA, 1985–2001.

Table 1.

Sample characteristics (N=3,614): CARDIA Year 15, 2000–2001

Variable	% or M (SD)	
Sex, % female	55.5%	
Race, % Black	47.0%	
Age, years, M (SD)	40.1	(3.6)
Education, years, M (SD)	14.9	(2.5)
Depressive symptoms, CES-D score, M (SD)	9.1	(7.9)
Smoking, cigarettes/day ^a , M (SD)	12.4	(9.3)
hsCRP, mg/L, M (SD)	3.2	(5.4)
SOD, U/mL, M (SD)	4.6	(2.2)
F2-isoprostanes, pmol/L, M (SD)	59.3	(32.4)
sP-selectin, ng/L, M (SD)	36.8	(11.2)
sICAM1, ng/L, M (SD)	154.9	(44.9)

^a Cigarettes per day reported among current smokers at Year 15, n=797 (22.1% of sample).

Abbreviations: M: mean. SD: standard deviation. hsCRP: high-sensitivity C-reactive protein. SOD: superoxide dismutase. sP-selectin: soluble P-selectin, sICAM1: soluble intercellular adhesion molecule-1.

Least squares mean (standard error) results of biomarkers by depressive symptoms trajectory and smoking trajectory in main effects models: CARDIA, 1985–2001

Table 2.

	Inflammation		Oxidative stress		Endothelial dysfunction	
	hsCRP (mg/L)	SOD (U/mL)	F2-isoprostanes (pmol/L)	sP-selectin (ng/L)	sICAM1 (ng/L)	
CES-D trajectory	$p<.001$	$p=.58$	$p=.022$	$p=.21$	$p=.028$	
No depressive symptoms (ref)	2.98 (0.14)	4.68 (0.06)	57.94 (0.89)	36.96 (0.31)	158.06 (1.22)	
Subthreshold depressive symptoms	3.55 (0.17)	4.69 (0.08)	61.20 (1.08)	37.78 (0.38)	161.63 (1.49)	
Decreasing depressive symptoms	3.07 (0.53)	4.27 (0.26)	67.03 (3.59)	38.11 (1.27)	159.29 (4.94)	
Increasing depressive symptoms	4.34 (0.34)	4.75 (0.16)	58.87 (2.26)	38.51 (0.79)	167.66 (3.07)	
High depressive symptoms	3.31 (0.78)	4.81 (0.39)	58.22 (5.43)	37.83 (1.93)	162.31 (7.48)	
CPD trajectory	$p=.45$	$p=.55$	$p=.002$	$p<.001$	$p<.001$	
Nonsmokers (ref)	3.35 (0.22)	4.56 (0.11)	58.31 (1.52)	36.97 (0.54)	151.77 (2.09)	
Quitters	3.41 (0.35)	4.67 (0.17)	56.93 (2.30)	36.55 (0.82)	149.34 (3.17)	
Light smokers	3.36 (0.32)	4.53 (0.16)	60.44 (2.18)	37.66 (0.77)	159.86 (3.01)	
Moderate smokers	3.26 (0.30)	4.75 (0.14)	63.06 (1.98)	38.13 (0.70)	171.23 (2.72)	
Heavy smokers	3.88 (0.32)	4.68 (0.15)	64.51 (2.14)	39.88 (0.76)	176.75 (2.94)	

Values are least squares mean (standard error) from linear regression models evaluating the main effects of CES-D trajectory or CPD trajectory. The p -values indicate the significance of the overall main effect term within each model. **Bold** indicates significant contrasts ($p<.01$), relative to the reference category (CES-D trajectory: No depressive symptoms; CPD trajectory: Nonsmokers) within significant ($p<.01$) main effects of CES-D trajectory or CPD trajectory.

Abbreviations: CES-D: Centers for Epidemiologic Studies – Depression scale. CPD: cigarettes per day. hsCRP: high-sensitivity C-reactive protein. SOD: superoxide dismutase. sP-selectin: soluble P-selectin. sICAM1: soluble intercellular adhesion molecule-1. Ref: reference.