ORIGINAL ARTICLE

Negative Emotions and 3-Year Progression of Subclinical Atherosclerosis

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Context: Although depression, anxiety, and hostility/anger have each been associated with an increased risk of coronary artery disease, these overlapping negative emotions have not been simultaneously examined as predictors of the progression of subclinical atherosclerosis.

Objective: To evaluate the relative importance of depressive symptoms, anxiety symptoms, and hostility/anger in predicting subclinical atherosclerotic progression over a 3-year period.

Design/Setting: The Pittsburgh Healthy Heart Project, an ongoing prospective cohort study of healthy, older men and women from the general community. At baseline, questionnaires were administered to assess depressive symptoms, anxiety symptoms, hostility, anger experience, and anger expression. Mean carotid intima-media thickness was assessed by B-mode ultrasonography during the baseline and 3-year follow-up visits.

Participants: Of the 464 adults enrolled in the project, 324 (69.8%) were included in this report because they had complete baseline and follow-up data.

Main Outcome Measure: Three-year change in mean carotid intima-media thickness.

Results: Regression analyses indicated that higher depressive symptoms at baseline were associated with greater 3-year change in carotid intima-media thickness (ΔR^2=0.026, P=.002), even after taking into account demographic factors, cardiovascular risk factors, medication use, medical conditions, and other correlated negative emotions. Measures of anxiety symptoms, hostility, anger experience, and anger expression were each unrelated to intima-media thickness change. Post hoc analyses examining depressive symptom clusters showed that the somatic-vegetative symptoms of depression (ΔR^2=0.027, P=.002), but not the cognitive-affective symptoms, were positively associated with intima-media thickness change.

Conclusion: Our findings suggest that the somatic-vegetative features of depression, but perhaps not anxiety and hostility/anger, may play an important role in the earlier stages of the development of coronary artery disease.

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CONSIDERABLE EVIDENCE from prospective studies suggests that individual differences in the experience and expression of various negative emotions—ie, depression, anxiety, and hostility/anger—are associated with an increased risk of coronary artery disease (CAD) in initially healthy populations.[1] A limitation of this literature, however, is that most investigations have examined the influence of a single negative emotion (eg, depression only) on CAD outcomes. As Suls and Bunde[1(p270)] recently discussed, this approach is not ideal because of the "appreciable construct and measurement overlap" that exists between these psychological factors. For instance, self-report measures of depression are highly correlated with anxiety measures (coefficients typically range from 0.45-0.75),[2] and self-report measures of hostility/anger are moderately correlated with both depression and anxiety measures (coefficients usually range from 0.25-0.50).[3-6] Because of this overlap, it is possible that all 3 of these negative emotions are independent risk factors, with each factor uniquely contributing to CAD development. It is also possible that 1 or more of these negative emotions are merely markers for another negative emotion that itself is a CAD risk factor (eg, hostility may predict future CAD simply by virtue of its relationship with depression). A third possibility is that these negative emotions reflect the same underlying factor (eg, negative affectivity[7]), and it is this common factor that is strongly associated with CAD risk and that accounts for the individual negative emotion–CAD relationships.

To identify the aspects of these overlapping negative emotions that may be involved in the pathogenesis of CAD, lon-

gitudinal studies are needed in which the effects of depression, anxiety, and hostility/anger on CAD outcomes are simultaneously examined. Unfortunately, to our knowledge, only 2 such investigations involving healthy individuals have been conducted. Chang and colleagues[8] found that men who reported the highest level of anger in response to stress were at increased risk of premature myocardial infarction 32 to 48 years later, even after adjustment for depression and anxiety measures. However, because parallel analyses were not reported for depression and anxiety, it is unclear whether these negative emotions were also independent predictors of premature myocardial infarction. In another sample of men, Kubzansky et al[9] observed that the shared aspects of depression, anxiety, and anger and the unique aspects of anxiety were both predictors of incident CAD, independent of one another and independent of the unique aspects of depression and anger. Those findings are difficult to interpret, however, given that the scales created for that study were not standard measures of negative emotions (eg, the depression measure assessed only hopelessness and suicidal ideation).

In addition to concurrently evaluating these overlapping negative emotions, another important direction for future research is to examine the stage(s) of CAD development during which these psychological factors may exert an influence. In most previous investigations of initially healthy persons, the outcome measure has been the incidence of clinical CAD, typically defined as the occurrence of a coronary event (eg, myocardial infarction or sudden cardiac death).[1] Because a coronary event is the final step of the pathogenesis of CAD,[10] it is presently not known whether depression, anxiety, and hostility/anger may play a role in the earlier stages of CAD development (eg, the initiation and progression of atherosclerosis) and/or the later stages (eg, the triggering of coronary events).[11] Noninvasive methods for measuring subclinical atherosclerosis, such as the assessment of carotid intima-media thickness (IMT) by ultrasonography,[12] can be useful for determining whether these negative emotions contribute to the earlier stages. To date, however, few studies have investigated the potential links between depression, anxiety, and hostility/anger and subclinical atherosclerotic progression,[13-17] and none has examined more than 1 of these negative emotions at the same time. Accordingly, we simultaneously evaluated the relative importance of depressive symptoms, anxiety symptoms, and hostility/anger in predicting 3-year change in carotid IMT among healthy, older men and women.

METHODS

PARTICIPANTS

Participants were healthy, older adults who volunteered to participate in the Pittsburgh Healthy Heart Project, an ongoing prospective cohort study examining biobehavioral factors as predictors of subclinical atherosclerosis. This study received the approval of the institutional review board at the University of Pittsburgh. Participants provided written informed consent and were paid $450. Recruitment strategies included mass mailings, media advertisements, and posters placed throughout the community. Major inclusion criteria were age (50-70 years) and menopausal status (women were required to be perimenopausal or postmenopausal, defined as the absence of menses during the past 6 months). Individuals were not enrolled if they reported a history of chronic medical disorders (including symptomatic cardiovascular disease), although persons with diabetes not taking insulin were included. Individuals were also not enrolled if they reported (1) lipid-lowering or antihypertensive medication use during the past year, (2) regular use of medications with autonomic effects (eg, antihistamines/decongestants or dietary aids), or (3) excessive alcohol consumption (≥5 drinks, >3 times per week). In addition, persons with systolic blood pressure greater than 180 mm Hg or diastolic blood pressure greater than 110 mm Hg were not enrolled. Of the 464 enrolled adults, 360 completed baseline and follow-up assessments of carotid IMT. We excluded those who underwent carotid endarterectomy during the follow-up interval (n=1) and those who had missing data for the variables listed in **Table 1** (n=35), leaving a final sample of 324 adults.

MEASURES AND PROCEDURES

Overview

During the baseline phase of the Pittsburgh Healthy Heart Project, participants attended 11 visits during a 5-month period in the following order: a medical screen, 3 visits for ambulatory monitoring training and questionnaire assessments, 1 visit for cardiovascular reactivity testing, 2 visits for ultrasound assessments, and 4 visits for additional ambulatory monitoring training and questionnaire assessments (**Figure 1**). At 6, 18, and 30 months after baseline, participants were interviewed by telephone to assess changes in their medical history and medication use. Approximately 3 years after baseline, participants attended 2 follow-up visits, during which the ultrasound assessments were repeated and a medical update was completed.

Demographic Factors

Data regarding age, sex (0, male; 1, female), race/ethnicity (0, white; 1, nonwhite), and education level (1, high school or less; 2, technical school or some college; 3, bachelor's degree; 4, master's degree or higher) were obtained from a questionnaire administered at the medical screen (Table 1). Participants were asked to choose from the following race/ethnicity categories: white, black, Asian, Hispanic, and other. Because only 6 individuals selected the Asian, Hispanic, or other categories, race/ethnicity was coded as a binary variable.

Cardiovascular Risk Factors

Participants underwent a blood pressure assessment, anthropometric measurements, and a blood draw at the medical screen. They were instructed to abstain from food and caffeine for 12 hours before this visit. Following American Heart Association guidelines,[18] 3 blood pressure readings were taken at 2-minute intervals with a standard mercury sphygmomanometer. Systolic and diastolic blood pressure were computed as the mean of the last 2 readings. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Standard assays were performed to determine levels of serum total cholesterol, high-density lipoprotein cholesterol, and triglycerides. Low-density lipoprotein cholesterol level was calculated by the Friedewald equation.[19] Fasting serum glucose level was measured by standard colorimetry, and fasting serum insulin level was measured by radioimmunoassay. These cardiovascular risk factors were reassessed by the same methods at

Table 1. Characteristics of 324 Participants

Characteristic	Descriptive Statistics*	Correlation With Carotid IMT Change†
Demographic factors		
Age, y	60.6 ± 4.7	0.02
Sex, % female	50.6	–0.16‡
Race, % nonwhite	15.7	–0.10
Education level, %		0.02
High school or less	24.4	
Technical school or some college	25.9	
Bachelor's degree	22.5	
Master's degree or higher	27.2	
Cardiovascular risk factors at baseline		
SBP, mm Hg	129.5 ± 15.3	0.00
DBP, mm Hg	80.0 ± 9.3	0.03
BMI	27.8 ± 4.5	–0.01
LDL-C, mg/dL	132.5 ± 33.0	0.07
HDL-C, mg/dL	54.3 ± 15.6	–0.05
Triglycerides, mg/dL§	137.9 ± 76.3	0.05
Fasting glucose, mg/dL§	92.9 ± 14.6	0.03
Fasting insulin, μU/mL§	11.4 ± 4.8	0.03
Physical activity level, kcal/wk	959.5 ± 804.6	0.06
Tobacco use, %	9.9	0.07
Daily alcohol intake, g/d§	6.4 ± 9.9	0.18‡
3-y Change in cardiovascular risk factors		
SBP, mm Hg	–6.0 ± 10.7	0.07
DBP, mm Hg	–2.5 ± 6.6	–0.03
BMI	0.2 ± 1.8	0.03
LDL-C, mg/dL	–12.1 ± 31.1	–0.10
HDL-C, mg/dL	–0.8 ± 10.2	0.06
Triglycerides, mg/dL	–6.8 ± 67.7	–0.05
Fasting glucose, mg/dL	6.2 ± 17.4	0.06
Fasting insulin, μU/mL	1.3 ± 6.2	–0.07
Medication use variables, %		
HT use at baseline (women only)	49.4	–0.05
SSRI use at baseline	1.5	–0.09
Lipid-lowering medication use during follow-up	17.9	0.05
Antihypertensive medication use during follow-up	17.3	0.05
Diabetes medication use during follow-up	3.1	0.07
HT use during follow-up (women only)	51.8	–0.10
SSRI use during follow-up	4.3	–0.16‡
Time between carotid IMT assessments, y	3.0 ± 0.2	0.06
Negative emotion measures (range of scale)		
Beck Depression Inventory II (0-63)§	3.9 ± 3.9	0.14‖
Beck Anxiety Inventory (0-63)§	5.1 ± 4.9	0.00
Cook-Medley Hostility Scale (0-50)	13.4 ± 6.4	0.02
State-Trait Anger Expression Inventory		
Trait anger (10-40)§	15.2 ± 3.3	0.02
Anger-in (8-32)	14.9 ± 3.7	–0.07
Anger-out (8-32)	13.1 ± 2.9	0.07
Anger control (8-32)	24.8 ± 4.9	–0.01

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HT, hormone therapy; IMT, intima-media thickness; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SSRI, selective serotonin reuptake inhibitor.

SI conversion factors: To convert cholesterol values to millimoles per liter, multiply by 0.0259; glucose values to millimoles per liter, multiply by 0.0555; insulin values to picomoles per liter, multiply by 6.945; and triglyceride values to millimoles per liter, multiply by 0.0113.

*Continuous data are presented as mean ± SD and categorical data are presented as percentage.

†Adjusted for mean baseline IMT.

‡$P<.01$.

§Log transformed variable was used in computation of partial correlation.

‖$P<.05$.

the follow-up visits. Three-year change in systolic and diastolic blood pressure, body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, fasting glucose, and fasting insulin was computed by subtracting the baseline level from the follow-up level.

During the medical screen, participants also completed the Paffenbarger Physical Activity Questionnaire[20] and questionnaires assessing tobacco and alcohol use. To obtain an estimate of physical activity level, the number of blocks walked and stairs climbed per day reported on the Paffenbarger Physi-

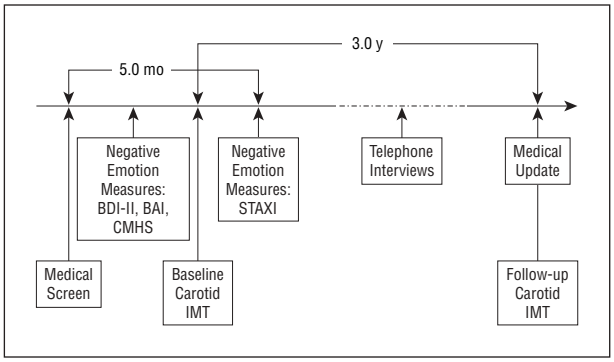

Figure 1. Timing of assessments. BAI indicates Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; CMHS, Cook-Medley Hostility Scale; IMT, intima-media thickness; and STAXI, State-Trait Anger Expression Inventory.

cal Activity Questionnaire were first converted to kilocalories per week and then summed (sports, leisure, and recreational activities were not included). Current tobacco use was coded as a binary variable (0, no; 1, yes). Daily alcohol intake in grams per day was computed by the quantity-frequency method.[21]

Table 1 shows descriptive statistics for the cardiovascular risk factors. Because the distributions for baseline triglycerides, fasting glucose, fasting insulin, and daily alcohol intake were positively skewed (skewness, 1.86, 4.12, 1.87, and 2.67, respectively), these variables were log transformed (skewness, 0.14, 2.48, –0.14, and 0.48, respectively).

Medical Conditions and Medication Use

Participants were asked about their medical history and medication use at the medical screen; at 6-, 18-, and 30-month telephone interviews; and at the follow-up visits. Using these data, we identified (1) participants who reported a history of diabetes or were uncertain of their diabetes status at baseline (n=7) and (2) participants who received a cardiovascular diagnosis (eg, myocardial infarction) or underwent a cardiovascular procedure (eg, bypass surgery) during the follow-up interval (n=14). These data were also used to create 7 medication use variables (0, no; 1, yes; see Table 1).

Negative Emotions

Participants completed self-report questionnaires on a computer to assess their experience and expression of various negative emotions. At the third baseline visit, participants were administered the Beck Depression Inventory II (BDI-II),[22] a widely used instrument that measures the severity of depressive symptoms, and the Beck Anxiety Inventory,[23] a questionnaire that assesses the severity of anxiety symptoms. On the BDI-II, participants were asked to rate the severity of their depressive symptoms during the past week instead of the past 2 weeks. Participants completed the Cook-Medley Hostility Scale[24] at the fourth baseline visit. The Cook-Medley Hostility Scale measures several components of hostility, including cynicism, hostile attributions, hostile affect, aggressive responding, and social avoidance. Because 1 item of the Cook-Medley Hostility Scale was accidentally omitted, the value for this item was imputed by taking the mean of the other 49 items. During the ninth baseline visit, participants were administered the State-Trait Anger Expression Inventory,[6] which consists of 5 subscales assessing the current experience of anger (state anger), the general tendency to experience anger (trait anger), the frequency with which anger is suppressed (anger-in) and expressed outwardly (anger-out), and the degree to which attempts are made to control the expression of anger (anger control). Because most participants (87.3%) reported no state anger and because the state anger subscale was not designed to be stable over time, it was not examined as a predictor of IMT change. The negative emotion measures that we used all have good psychometric properties, including moderate to high internal consistency, test-retest reliability, and construct validity.[22,25-27]

Table 1 displays descriptive statistics for the negative emotion measures. Because the distributions for scores on the BDI-II, Beck Anxiety Inventory, and trait anger subscale of the State-Trait Anger Expression Inventory were positively skewed (skewness, 1.30, 1.96, and 1.21, respectively), these variables were log transformed (skewness, –0.12, –0.26, and 0.39, respectively). Correlations between the negative emotion measures were generally in the small to moderate range (**Table 2**), indicating that these measures shared a modest yet significant amount of variance. The observed correlations were slightly smaller than those previously reported,[2-6] perhaps because the variability of some measures was less in our sample than in the comparison samples.

Carotid IMT

Carotid IMT is considered to be a noninvasive measure of subclinical atherosclerosis, as it is positively associated with the extent of coronary atherosclerosis and is an independent predictor of future coronary events.[12] Approximately 2 months after the medical screen, participants underwent baseline assessments of carotid IMT. B-mode ultrasound scanners (Toshiba SSA-270A and SSA-140A; Toshiba American Medical Systems, Tustin, Calif) were used to obtain digitized images of 6 segments of the carotid arteries: the distal 1 cm of the common carotid artery, the carotid bulb, and the proximal 1 cm of the internal carotid artery from both the left and right sides. An average of 3 years after the baseline assessment, carotid IMT was reassessed by the same methods. To avoid problems with reader drift over time, baseline and follow-up images were scored concurrently.

An automated edge detection system (AMS; Goteborg University, Gothenburg, Sweden)[28] was used to measure IMT, defined as the mean distance between the intima-lumen interface and the media-adventitial interface of the far wall. Baseline IMT (mean [SD], 0.761 [0.149] mm) and follow-up IMT (mean [SD], 0.851 [0.217] mm) were computed by averaging the IMT measures for the 6 carotid artery segments obtained during the baseline and follow-up assessments, respectively. Three-year change in IMT (mean [SD], 0.091 [0.141] mm) was calculated as mean follow-up IMT minus mean baseline IMT. Annualized carotid IMT progression rates observed in this study (all segments, 0.030 mm; common carotid, 0.012 mm; carotid bulb, 0.039 mm; internal carotid, 0.040 mm) were comparable, although slightly higher, than those found in past investigations,[29,30] possibly because our sample was older than previous samples.

STATISTICAL ANALYSIS

To evaluate the relative importance of various negative emotions in predicting 3-year change in carotid IMT, multiple regression analyses were performed. Mean baseline IMT was entered into each model in step 1. In step 2, control variables that were independent predictors of IMT change were entered into each model. Potential control variables were the variables listed in Table 1, as well as the first-order interactions for the demographic factors. To identify factors that were independent predictors of IMT change, each potential control variable was first entered into a separate model containing mean baseline IMT

Table 2. Correlations Between Negative Emotion Measures*

	BDI-II	BAI	CMHS	Trait Anger	Anger-In	Anger-Out
BDI-II†						
BAI†	0.42‡					
CMHS	0.22‡	0.16‡				
Trait anger†	0.19‡	0.19‡	0.32‡			
Anger-in	0.21‡	0.17‡	0.26‡	0.26‡		
Anger-out	0.04	0.10	0.11§	0.52‡	−0.07	
Anger control	−0.18‡	−0.15‡	−0.11§	−0.42‡	−0.04	−0.51‡

Abbreviations: BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; CMHS, Cook-Medley Hostility Scale.
*N = 324. Values are Pearson product-moment correlation coefficients.
†Log transformed.
‡$P<.01$.
§$P<.05$.

Table 3. Multiple Regression Analyses Predicting 3-Year Change in Carotid IMT

	B	SE B	95% CI for B	β	R^2	ΔR^2	ΔF
Step 1					0.015	0.015	4.91*
Mean baseline IMT	0.116	0.052	0.013 to 0.219	0.123*			
Step 2					0.103	0.088	6.19†
Age	0.005	0.002	0.001 to 0.009	0.162*			
Sex	−0.027	0.016	−0.059 to 0.005	−0.095			
Age × sex	−0.010	0.003	−0.016 to −0.003	−0.215†			
Baseline daily alcohol intake‡	0.041	0.016	0.010 to 0.073	0.147†			
SSRI use during follow-up	−0.104	0.037	−0.178 to −0.031	−0.151†			
Step 3§							
BDI-II‡	0.063	0.021	0.022 to 0.104	0.162†	0.128	0.026	9.35†
BAI‡	0.019	0.023	−0.025 to 0.063	0.046	0.105	0.002	0.70
CMHS	0.000	0.001	−0.002 to 0.002	0.004	0.103	0.000	0.01
Trait anger‡	−0.009	0.084	−0.175 to 0.157	−0.006	0.103	0.000	0.01
Anger-in	−0.002	0.002	−0.006 to 0.002	−0.057	0.106	0.003	1.12
Anger-out	0.003	0.003	−0.002 to 0.009	0.069	0.107	0.005	1.63
Anger control	0.000	0.002	−0.003 to 0.003	0.002	0.103	0.000	0.00

Abbreviations: B, unstandardized regression coefficient; BAI, Beck Anxiety Inventory; BDI-II, Beck Depression Inventory II; CI, confidence interval; CMHS, Cook-Medley Hostility Scale; IMT, intima-media thickness; SSRI, selective serotonin reuptake inhibitor.
*$P<.05$.
†$P<.01$.
‡Log transformed.
§Negative emotion measures were examined in separate models, each of which contained mean baseline IMT and the selected control variables. A Bonferroni correction was applied to the tests of the regression coefficients of the negative emotion measures.

only (see Table 1 for partial correlations). Potential control variables that were significant predictors ($P<.05$) were then simultaneously entered into the same model. Variables that remained significant or marginally significant ($P<.10$) were retained in the model; variables that became nonsignificant ($P\geq.10$) were removed. In step 3, scores on the BDI-II, Beck Anxiety Inventory, Cook-Medley Hostility Scale, and State-Trait Anger Expression Inventory subscales of trait anger, anger-in, anger-out, and anger control were first entered into separate models containing mean baseline IMT and the selected control variables. Because each negative emotion measure was examined in a separate model, a Bonferroni correction was applied to the tests of their regression coefficients to maintain a familywise type I error rate of 5% or less. All of the negative emotion measures were then simultaneously entered into the same model.

To ensure that diabetes did not account for any observed negative emotion–IMT change relationships, analyses were repeated after excluding participants who reported a history of diabetes or were uncertain of their diabetes status at baseline (n=7). To rule out the possibility that any observed relationships were driven primarily by individuals who developed a cardiovascular disease, analyses were also repeated after excluding participants who received a cardiovascular diagnosis or underwent a cardiovascular procedure during follow-up (n=14). In addition, interactions (cross-product terms) between each negative emotion measure and sex were tested to determine whether associations between these measures and IMT change varied between men and women.

Standard diagnostic procedures were performed for all analyses to assess for the presence of outliers, influential cases, nonnormally distributed errors, nonconstant error variance, nonlinearity, and collinearity.[31] No violations of assumptions were detected, though a small number of outliers (≤6 cases in each model) were identified. Because none of the outliers was also an influential case, they were not excluded from the analyses.

RESULTS

As shown in **Table 3**, regression analyses indicated that mean baseline IMT was positively related to 3-year change

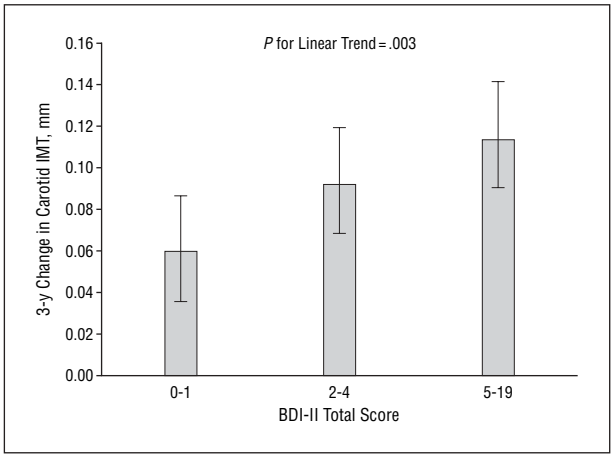

Figure 2. Mean 3-year change in carotid intima-media thickness (IMT) for participants in the lower, middle, and upper tertiles of the Beck Depression Inventory II (BDI-II) total score. Error bars represent 95% confidence intervals for the mean (N = 324).

in carotid IMT and accounted for 1.5% of the variance (step 1). Of the potential control variables, only the age × sex interaction, baseline daily alcohol intake, and selective serotonin reuptake inhibitor (SSRI) use during follow-up were independent predictors of IMT change. Thus, only these variables (and the main effects of age and sex) were included in the models (step 2). Follow-up analysis of the age × sex interaction showed that age was positively related to IMT change among men ($\beta = .164$, $P = .04$) but was negatively related among women ($\beta = -.187$, $P = .02$). In addition, higher daily alcohol intake at baseline was associated with greater change in IMT. Conversely, SSRI use during follow-up was associated with reduced IMT change, as mean 3-year change in carotid IMT was –0.009 mm for those who used an SSRI vs 0.095 mm for those who did not. Together, the selected control variables explained an additional 8.8% of the variance.

Separate regression analyses for each negative emotion measure indicated that BDI-II score was positively associated with 3-year change in carotid IMT, explaining 2.6% of the variance beyond that accounted for by baseline IMT and the selected control variables (step 3). In contrast, Beck Anxiety Inventory score, Cook-Medley Hostility Scale score, and State-Trait Anger Expression Inventory subscale scores of trait anger, anger-in, anger-out, and anger control were each unrelated to IMT change. When all 7 negative emotion measures were simultaneously entered into the same model, BDI-II score remained a significant predictor ($\beta = .206$, $P = .001$). The BDI-II score also remained a significant predictor after excluding participants who reported a history of diabetes or were uncertain of their diabetes status at baseline ($\beta = .154$, $P = .005$) and after excluding those who received a cardiovascular diagnosis or underwent a cardiovascular procedure during follow-up ($\beta = .166$, $P = .002$). No significant interactions between the negative emotion measures and sex were detected (all $P > .15$). To further illustrate the observed relationship, participants were classified into tertiles on the basis of their BDI-II score. As can be seen in **Figure 2**, mean 3-year change in carotid IMT (adjusted for baseline IMT and the selected control variables) was 0.061 mm for participants in the lower tertile, 0.094 mm for those in the middle tertile, and 0.116 mm for those in the upper tertile (P for linear trend = .003).

To explore whether particular clusters of depressive symptoms were more strongly associated with 3-year change in carotid IMT than were others, post hoc analyses were performed. Two BDI-II subscale scores were computed on the basis of the results of Dozois et al[32]: a cognitive-affective score (sum of items 1-3, 5-9, 13, and 14) and a somatic-vegetative score (sum of items 4, 10-12, and 15-21). The cognitive-affective subscale (mean score [SD], 1.1 [1.7]) consisted of items assessing the cognitive and emotional symptoms of depression (eg, sadness, pessimism, and indecisiveness), whereas the somatic-vegetative subscale (mean score [SD], 2.9 [2.8]) primarily included items assessing the physical symptoms (eg, anhedonia, fatigue, and sleep/appetite disturbance). Both subscale scores were log transformed to reduced positive skewness. Separate regression analyses for each subscale score indicated that the somatic-vegetative score ($\beta = .165$, $P = .002$), but not the cognitive-affective score ($\beta = .061$, $P = .26$), was positively associated with IMT change in the presence of baseline IMT and the selected control variables. The somatic-vegetative score explained approximately the same amount of variance as did the BDI-II total score ($\Delta R^2 = 0.027$). In addition, the somatic-vegetative score remained a significant predictor when both BDI-II subscales and the other 6 negative emotion measures were simultaneously entered into the same model ($\beta = .184$, $P = .003$), after excluding participants who reported a history of diabetes or were uncertain of their diabetes status ($\beta = .153$, $P = .005$), and after excluding those who received a cardiovascular diagnosis or underwent a cardiovascular procedure during follow-up ($\beta = .165$, $P = .003$). The interactions between the BDI-II subscales and sex were nonsignificant (both $P > .50$).

COMMENT

The present study simultaneously examined overlapping negative emotions as predictors of subclinical atherosclerotic progression among healthy, older adults. We found that mild to moderate depressive symptoms, as assessed by the BDI-II, were associated with greater 3-year change in carotid IMT. In contrast, measures of anxiety symptoms, hostility, anger experience, and anger expression were each unrelated to IMT change. Post hoc analyses showed that the BDI-II somatic-vegetative subscale score, but not the cognitive-affective subscale score, was predictive of IMT change, which demonstrates that this symptom cluster was responsible for the association with the BDI-II total score. The observed relationships were not accounted for by potentially confounding factors (baseline IMT, demographic factors, cardiovascular risk factors, medication use, and medical conditions) and remained significant after adjustment for other correlated negative emotions. Taken together, our results indicate that depression, but perhaps not anxiety and hostility/anger, may be involved in the initia-

tion and/or progression of atherosclerosis. More specifically, our findings suggest that the somatic-vegetative features of depression that are not shared with other negative emotions may play an important role in the earlier stages of CAD development.

Although this study is the first, to our knowledge, to report an association between depressive symptoms and IMT change, our results are consistent with the findings of past investigations examining the effect of depression-related factors on subclinical atherosclerotic progression.[13,14,16] Interestingly, each of those studies found that a cognitive-affective aspect of depression (ie, discontent, hopelessness, and pessimism) predicted IMT change. Thus, it could be argued that those previous findings are in agreement with ours on a broad construct level but contradict ours on a specific component level. However, because the somatic-vegetative aspects of depression were not examined in those studies, it is not possible to determine whether the observed relationships were specific to the cognitive-affective aspects. Our results also are in line with those of studies reporting positive associations between depressive disorders or symptoms and measures of subclinical atherosclerosis obtained at one point in time.[33-37] Finally, the present findings contribute to the growing body of evidence supporting a link between depression and clinical CAD[1] and suggest that depression may predict future coronary events, in part because of its involvement in early atherosclerotic processes. It should be noted that, although the results of Kubzansky and colleagues[9] appear to be at odds with ours, the absence of a significant link between the unique aspects of depression and incident CAD in their study may have resulted from the limited scope and restricted variability of their depression measure.

Several plausible mechanisms could underlie the observed relationship between depressive symptoms and IMT change. For instance, depression has been associated with pathophysiologic changes thought to be involved in atherosclerosis, including autonomic nervous system dysfunction,[38] hypothalamic-pituitary-adrenal axis dysregulation,[39] enhanced inflammatory processes,[40] and altered platelet function.[41] It is unlikely, however, that traditional cardiovascular risk factors mediate the observed relationship, as it persisted after these factors were taken into account. The observed relationship might also be explained by a third factor that could cause both increased depressive symptoms at baseline and greater IMT progression. One such factor is inflammation stemming from subclinical atherosclerosis, given that proinflammatory cytokines can produce behavioral changes similar to the symptoms of depression.[42] Another possible third factor is subclinical cerebrovascular disease, which has been hypothesized to be involved in the etiology of late-onset depression.[43] Neither of these potential third factors, however, appears to be a likely explanation for our findings. Because our analyses were adjusted for baseline IMT (which can be considered a general marker of systemic atherosclerosis given that it predicts coronary events, stroke, and peripheral vascular disease[44-50]), it is likely that we adequately controlled for the potential influence of subclinical cardiovascular disease on baseline depressive symptoms.

It is unclear why the somatic-vegetative symptoms of depression predicted subclinical atherosclerotic progression, whereas the cognitive-affective symptoms did not. One possibility is that there may be stronger links between the somatic-vegetative symptoms and the mechanisms underlying the depression-CAD relationship. Another possibility is that older individuals, such as those in our sample, may be more likely to report the somatic-vegetative symptoms. Recent evidence suggests that this may indeed be the case. Kim and colleagues[51] found that depressed patients 60 years or older endorsed more somatic symptoms and fewer cognitive symptoms on the BDI than did depressed patients younger than 60 years. Our data also support this idea, as the cognitive-affective subscale had a smaller mean and standard deviation than did the somatic-vegetative subscale. Thus, the cognitive-affective score may not have predicted IMT change because of the restricted variability of this subscale.

Our findings pertaining to the influence of anxiety and hostility/anger on subclinical atherosclerotic progression contrast with existing evidence. Paterniti and colleagues[17] found that sustained anxiety predicted 4-year IMT progression, and Julkunen et al[15] reported that cynical distrust (a component of hostility) and anger suppression were both positively associated with 2-year IMT progression. In addition, positive associations have been reported between hostility/anger and measures of subclinical atherosclerosis obtained at one point in time.[52-56] Potential reasons for these discrepant findings include differences in the negative emotion measures used (eg, see Paterniti et al[17]) and the characteristics of the participants studied (eg, see Julkunen et al[15]). Furthermore, because neither depressive disorders nor symptoms were assessed in these previous studies, it is possible that measures of anxiety and hostility/anger may have been acting as markers for depression in these instances. Even though our findings suggest that anxiety and hostility/anger may not be involved in early atherosclerotic processes, they are not necessarily inconsistent with the evidence linking these factors with future CAD,[1,8,9] as these negative emotions could play a role in later stages of CAD development.[57]

Although this study makes important contributions to the literature, a few limitations should be noted. First, because of an oversight while constructing the computerized version of the BDI-II, participants were asked to rate the severity of their depressive symptoms during the past week (the time frame for the original BDI) instead of during the past 2 weeks (the time frame for the BDI-II). This irregularity creates some minor interpretation problems, but its most important influence is probably the underestimation of the true BDI-II score, as individuals tend to score lower on the original BDI than on the BDI-II.[32] This, in turn, could have weakened the relationship between depressive symptoms and IMT change by reducing variability in the BDI-II scores. Second, a number of traditional cardiovascular risk factors were not associated with IMT change in the present sample. Significant relationships, however, were detected between traditional risk factors (ie, systolic and diastolic blood pressure) and carotid IMT in cross-sectional analyses.[58] In addition, we observed an inverse relationship between SSRI

use during follow-up and IMT change, which is consistent with recent evidence that treatment with SSRIs may have beneficial cardiovascular effects.[59,60] Several factors may have limited our ability to detect relationships between traditional risk factors and IMT change; these include the overall health of the sample, the relatively brief follow-up period, and the general stability of these risk factors over time. Moreover, it has been found that longitudinal associations between traditional risk factors and carotid IMT are generally not as strong as cross-sectional associations.[29] Third, because this study included only healthy, older individuals, our findings may not be generalizable to younger populations or to older populations in which chronic medical disorders are prevalent. Therefore, it is necessary that our results be replicated in population-based studies with less stringent inclusion criteria.

In sum, our findings indicate that the somatic-vegetative features of depression may play an important role in the initiation and/or progression of atherosclerosis, although anxiety and hostility/anger may not. Our results also highlight a key advantage of simultaneously examining overlapping negative emotions: this approach will help us to identify the deleterious aspects of these multidimensional factors. Identifying these components, in turn, may provide insights into the mechanisms underlying the negative emotion–CAD relationships and may facilitate the development of focused interventions designed to reduce the CAD risk of individuals prone to experience negative emotions.

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