Trait Anger and the Metabolic Syndrome Predict Progression of Carotid Atherosclerosis in Healthy Middle-Aged Women

K. Räikkönen, PhD, Karen A. Matthews, PhD, Kim Sutton-Tyrrell, DrPH, and Lewis H. Kuller, MD, DrPH

Objective: Hostility may predict coronary heart disease morbidity and mortality, as well as the metabolic syndrome. We tested to see if high levels of the attitudinal and emotional aspects of hostility lead to progression of carotid atherosclerosis in women and if the metabolic syndrome is a mediator of the association. **Methods:** Two hundred nine healthy women were followed during the perimenopausal and postmenopausal periods. Carotid artery ultrasound scans measured intima-media thickness (IMT) an average 7.4 (SD = 0.9, range 4.2–10.8) and 10.5 years (SD = 1.1, range = 6.9–13.0) after baseline. Hostility was measured at baseline and at the first carotid scan with Spielberger Trait Anger (being angry frequently) and Anger In (suppressing angry feelings) scales, and the Cook-Medley Hostility Inventory (hostile, cynical attitudes toward others). Metabolic syndrome was measured at the study entry and through the second carotid scan. **Results:** Baseline Trait Anger scores predicted an increase in IMT across 3 years ($p < .05$) and predicted the risk for developing the metabolic syndrome ($p < .05$). The risk for developing the metabolic syndrome, in turn, predicted an increase in IMT across 3 years ($p < .05$). Anger suppression and cynical attitudes were not associated with progression of carotid atherosclerosis. **Conclusion:** Anger predicts progression of carotid atherosclerosis, and the metabolic syndrome may mediate this association. Women who experience angry feelings frequently may benefit from interventions aimed at reducing anger and reducing the metabolic syndrome components early in the natural history of atherosclerosis. **Key words:** anger, carotid atherosclerosis, metabolic syndrome, women.

CHD = coronary heart disease; **IMT** = intima-media thickness; **HWS** = healthy women study; **BP** = blood pressure; **DBP** = diastolic blood pressure; **SBP** = systolic blood pressure; **HDL-C** = high-density lipoprotein cholesterol; **ANCOVA** = univariate analysis of covariance; **RMSEA** = root mean square error of approximation.

INTRODUCTION

Hostility is a multidimensional construct that includes frequent and intense feelings of anger; mistrustful, cynical attitudes; and overt aggressive acts. A meta-analytic review of studies published through 1995 concluded that hostility is associated with coronary heart disease (CHD) morbidity and mortality, as well as all-cause mortality (1). Interview ratings of hostile behaviors show more consistent association with CHD incidence, and self-reports of hostile attitudes show more consistent associations with all-cause mortality. Hemingway and Marmot (2) reviewed epidemiological studies that used healthy population-based samples (n > 500), prospective study designs, psychosocial instruments used in at least in two different study populations, and measured CHD via myocardial infarction or CHD death. They concluded that the global hostility construct might have a potential etiological role in predicting CHD (2), but the existing evidence is not robust enough to establish a role for hostility in the development of CHD (3).

The inconsistent findings may reflect differences in instruments used for measuring hostility. Also, the findings may mirror the importance of some components of hostility (1,4). A recent study demonstrated that ratings of hostile behaviors during the Type A interview predicted cardiovascular mortality over 16 years in high-risk men participating in the Multiple Risk Factor Intervention Trial (4). Further, a small but growing number of studies show that angry feelings may be associated with CHD morbidity and mortality. In the Framingham Study, 45- to 64-year-old women who did not discuss anger and men who did not show anger were at increased risk for developing CHD over 8 years (5); in the Normative Aging Study (6), a composite score of expressing anger frequently and intensely and problems in controlling anger among 61-year-old men predicted CHD over 7 years; intense and frequent feelings of anger (7) and an angry temperament (8) in 45- to 64-year-old black and white men and women enrolled in Atherosclerosis Risk in Communities Study predicted CHD over 53 months; and in the Johns Hopkins Precursors Study (9), angry responses to stress predicted premature CHD before the age of 55 in men over a median follow-up of 36 years.

The advent of techniques to measure the extent of subclinical atherosclerosis has facilitated studying relationships of risk factors and atherosclerosis earlier in the disease process before the onset of clinical events and death. Carotid atherosclerosis measured by B-mode ultrasound scans of intima-media thickness (IMT) is correlated with coronary atherosclerosis and predicts increased risk of stroke and myocardial infarction (10,11). Elevated IMT scores are correlated with angry feelings among Japanese women and men (12) and with hostile attitudes among American women, but only among those with a high familial risk for CHD (13). To date, only one study has tested whether hostility predicts progression of carotid atherosclerosis. Among 119 middle-aged men of the Kuopio Ischemic Heart Disease Risk Factor Study, cynical, mistrustful attitudes and controlling angry feelings predicted an increase in carotid IMT across 2 years (14). We previously reported that among healthy women, self-reported angry feelings and hostile attitudes predicted carotid IMT 1.5 to 10 years later (15). The current study tested whether, in a subset of the same sample from the Healthy Women Study (HWS) who had repeat carotid ultrasounds, angry feelings and hostile attitudes also predicted greater progression in carotid IMT across 3 years.

From the University of Helsinki, Department of Psychology, Helsinki, Finland (K.R.); and the University of Pittsburgh, Department of Psychiatry (K.A.M.), Department of Epidemiology (K.S.-T.), and Department of Psychology (L.H.K.), Pittsburgh, PA.

Address correspondence and reprint requests to Karen A. Matthews, PhD, University of Pittsburgh, 3811 O'Hara Street, Pittsburgh, PA 15213. E-mail: matthewska@upmc.edu

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Components of hostility are not likely to affect atherosclerosis directly but may rather be mediated via multiple biological, physiological, or behavioral processes (1,2,4). Obesity, glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and blood pressure, independently and collectively composing the metabolic syndrome, predict higher levels and progression of carotid atherosclerosis (16,17). We have recently shown among the HWS participants that angry feelings are related to CHD risk factors (18,19) and predict the risk for developing the metabolic syndrome during the peri- and postmenopausal years (20). Accordingly, we tested if the metabolic syndrome risk mediated any effects of anger and hostile attitudes on progression of carotid atherosclerosis.

METHODS

Study Population

Participants were drawn from the HWS, an ongoing prospective study of the changes in behavioral and biological characteristics of women during the peri- and postmenopausal years. In 1983 to 1984, 541 participants (90% Caucasian) were recruited from a random sample of licensed drivers in Allegheny County, Pennsylvania (21,22). They were aged 42 to 50 years at study entry, menstruating within the past 3 months and not taking hormone replacement, DBP $<$100 mm Hg, not surgically menopausal, not diagnosed with diabetes or with hypertension, and not taking thyroid, lipid-lowering, or psychotropic medications. The institutional review board at the University of Pittsburgh approved this project; all subjects gave informed consent.

Women underwent baseline clinic examinations and returned cards monthly to indicate whether they had menstruated. After 12 successive months without menstruating, women returned for a follow-up examination and then every several years thereafter. Carotid ultrasound measures were added to the protocol for women who participated in examinations 5 and 8 years postmenopause starting in 1993. Of the 308 women scanned initially, 209 women returned for a follow-up scan an average 3.0 years later (SD = 0.7; range 0.9 to 5.4).

Measurement of waist circumference, one of the metabolic syndrome components, was added for all participants at the first follow-up examination of the HWS, an average 2.8 (SD = 0.6, range 0.7–6.3) years from study entry. Therefore, the first follow-up examination was used as the starting point for the current analyses, hereafter labeled as baseline. The baseline was 7.4 years (SD = 0.9, range 4.2–10.8) before the first carotid scans and 10.5 years (SD = 1.1, range 6.9–13.0) before the second scans. Data on Trait Anger and Anger In scores were available from 203 women at the baseline and 207 women at the first carotid scans. The Cook-Medley measure was added later to the HWS protocol in 1991; Cook-Medley data were available from 203 women at the time of the first carotid scan. Thus, the analytic sample was composed of 203 women when progression of carotid atherosclerosis was predicted from the anger and hostile attitudes measured at baseline or at first carotid scans. Data on the metabolic syndrome were available from 201 to 205 women at baseline, and of those, 198 women had metabolic syndrome data available at a follow-up examination up to the first and the second carotid scans.

Women who had two carotid examinations were younger (M(SD) = 58.0(1.6) vs. 59.3(2.3), $p < .001$), had become menopausal at a later age (M(SD) = 52.6(2.2) vs.51.7(3.0), $p < .001$), and had lower systolic blood pressure (M(SD) = 118.0(15.2) vs. 123.7(20.8), $p < .002$) at the time of the first scan compared with women who had only one scan. No other significant differences existed between women with and without a second scan in the other study variables at the time of the first scan or the baseline of the current study (p's $> .07$).

Measurement of Carotid Arteries

B-mode ultrasound scans of the carotid artery were obtained using a scanner with a 5 MHz linear array imaging probe, with the same equipment at both scans. Trained readers measured the average IMT across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of average IMT. Maximal IMT measures from each of the five locations were also averaged. We used a modified computerized reading program developed for the Cardiovascular Health Study (11).

Reproducibility of IMT was assessed in five women who underwent two ultrasound examinations within 1 week. Each time, two separate sonographers scanned the women, and two readers scored each scan. When accounting for sonographer and reader variation, the intraclass correlation was 0.86 for average IMT.

Metabolic Syndrome

Blood draw was collected in the morning after a 12-hour fast. Glucose was analyzed by enzymatic assay (Yellow Springs Glucose Analyzer, Yellow Springs, OH), triglycerides and total HDL-C were measured in the lipid laboratory of the Graduate School of Public Health, which has been certified by the Centers for Disease Control and Prevention, Atlanta, GA; waist was measured at the smallest circumference; BP was measured three times on two occasions 2 hours apart with a random zero muddler sphygmomanometer, the final overall reading being the average of the last two readings of these two assessments. The metabolic syndrome was defined (22) as the presence of three or more of the following: (a) fasting glucose $\geq$110 mg/dl; (b) triglycerides $\geq$150 mg/dl; (c) HDL-C $<$50 mg/dl; (d) waist circumference $>$88 cm, and (e) systolic blood pressure $\geq$130 mm Hg and diastolic blood pressure $\geq$85 mm Hg.

Hostility Measures

The Spielberger Trait Anger scale measures intensity and frequency of angry feelings (23). Participants rated themselves on 10 items, such as "I have a fiery temper," and "I fly off the handle," using a four-point scale. Two subscales of four items each can also be calculated, angry temperament (eg, I am quick tempered), and angry reaction (eg, I get angry when I am slowed by others' mistakes) (8). The Anger In scale, which is derived from the Spielberger Anger Expression scale, measures a tendency to suppress angry feelings (24). The participant on a four-point scale rated the eight items, such as "I keep things in," "I boil inside, but I do not show it." The Cook-Medley Hostility scale measures cynical and mistrustful attitudes toward others (25). The 50 items, such as "It is safer to trust nobody," "Most people make friends because friends are likely to be useful to them," were rated by the participants as being true or false. In the current sample of women, the test-retest reliability over 3 years was 0.87 and 0.76, respectively, for Trait Anger and Anger In (n = 209) and 0.88 for the Cook-Medley hostile attitudes scale (n = 88). The Cronbach's α coefficients for internal consistency of the scales range from 0.74 to 0.85 (23–25).

Behavioral Covariates

Use of hormone replacement therapy was assessed via self-report. Cigarette smoking was measured by current status of smoking (yes/no) and alcohol intake by the amount of alcohol per day converted into grams of absolute alcohol (g/day). The Paffenbarger activity questionnaire was used to measure kilocalories per week spent in leisure-time activity (26).

Statistical Analyses

Multiple linear regression analyses and univariate analyses of covariance tested whether the components of hostility, measured at the baseline (Trait Anger, Anger In) and at the time of the first carotid scan (Trait Anger, Anger In, and Cook-Medley hostile attitudes) predict change in mean and maximum IMT across 3 years. Univariate analyses of covariance (ANCOVA) were used to illustrate significant findings using percent change of mean and maximum IMT across 3 years as the dependent variables.

Path analyses (MPLUS) (27) tested whether hostility components predicted progression of carotid atherosclerosis via the risk for developing the metabolic syndrome during the follow-up interval. Path analysis is a method that allows one to test whether a hypothesized set of relationships, ie, the model, fits the data. In path analyses, many multiple regressions are tested

simultaneously. We used the maximum likelihood estimation method with robust standard errors and evaluated the goodness of fit of the path model by χ^2 statistic ($p > .05$), comparative fit index (CFI >0.90), and root mean square error of approximation (RMSEA). RMSEA below 0.05 indicates a close fit (28) and RMSEA from 0.05 to 0.08 indicates adequate fit (29). Analyses of change were adjusted statistically for baseline values. Additional covariates were age at the time of the measurement of anger and hostility and duration in time between the carotid scans.

RESULTS

Table 1 shows that at the first carotid scan mean IMT and maximum IMT in the sample were 0.77 and 1.00 mm and increased an average of 0.03 mm (4.8%; $t = 6.85$, $p < .001$) and 0.01 mm (2.2%, $t = 1.93$, $p < .054$) across the 3-year interval, respectively. Table 2 presents the sample characteristics. Women averaged 50.6 years at baseline and 58.1 years at the time of the first carotid scans an average 7.4 years later. Up to the first carotid scans, 25 women had developed the metabolic syndrome; up to the second carotid scans 30 women had developed the metabolic syndrome; 160 remained free from the metabolic syndrome over the follow-up. Six women had the metabolic syndrome both at baseline and during the follow-up, and two women had the metabolic syndrome at baseline only. Because of the small group size, they were excluded from all further analyses.

We tested whether the behavioral covariates, age, and the follow-up time significantly predicted progression of carotid atherosclerosis. Of the covariates, progression of carotid atherosclerosis was predicted by current smoker status at the first carotid scan (mean and maximum IMT, p's $< .02$), and longer duration in time between the first and second carotid scans (p's $< .003$). We also tested whether the metabolic syndrome status over the follow-up predicted progression. Women who developed the metabolic syndrome by the first carotid scan ($n = 25$) and by the second carotid scan ($n = 30$) had greater progression of carotid atherosclerosis relative to women who remained free from it over the follow-up (mean IMT: β's >0.13, $t = 1.97$, $p < .05$; maximum IMT: $\beta = 0.15$, $t = 2.45$, $p < .05$).

Associations Between Hostility and Mean and Maximum IMT

Pearson correlations between the hostility scores and mean and maximum IMT levels at first and second carotid scans showed that baseline Trait Anger was significantly correlated with a higher level of mean IMT measured at the time of the second scan ($r = 0.15$, $p < .035$); and Trait Anger measured at the first scan was significantly correlated with mean IMT, $r = 0.20$ and 0.20 (p's $< .004$), and maximum IMT, $r = 0.17$ and 0.16 (p's $< .023$), respectively, at first and second carotid scan. Anger In and Cook-Medley hostile attitudes were not significantly correlated with levels of mean and maximum IMT at either examination (p's $> .074$), except Cook-Medley hostile attitudes was correlated with mean IMT measured at the first carotid scan ($r = 0.14$, $p = .04$).

Baseline Trait Anger predicted an increase in mean IMT over 3 years, $\beta = 0.13$, $t = 2.02$, $p < .05$. Association with maximum IMT was not significant ($p > .33$). Trait Anger measured at the time of the first carotid scans did not significantly predict progression of carotid atherosclerosis (p's > .11). To illustrate the significant association of baseline Trait

TABLE 1. Mean Values (SD) of the Carotid Measures

Intima-media thickness (mm)	*N*	M (SD)
Mean at		
First scan	209	0.77 (0.1)
Second scan	209	0.80 (0.1)
Difference (second scan–first scan)	209	0.03 (0.1)
Difference (second scan–first scan), %	209	4.8 (8.9)
Maximum at		
First scan	209	1.00 (0.2)
Second scan	209	1.02 (0.2)
Difference (second scan–first scan)	209	0.01 (0.1)
Difference (second scan–first scan), %	209	2.2 (10.4)

TABLE 2. Characteristics of the Sample at Baseline and at First Carotid Scans

Characteristic	*N*	M (SD)
Age, y		
Baseline	208	50.6 (1.4)
First scan	209	58.1 (1.6)
Menopause	209	52.6 (2.2)
HDL-cholesterol, mg/dl		
Baseline	201	58.5 (14.6)
First scan	208	60.6 (15.9)
Triglycerides, mg/dl		
Baseline	201	87.5 (46.9)
First scan	208	116.2 (64.1)
Fasting Glucose, mg/dl		
Baseline	202	87.6 (9.7)
First scan	208	90.0 (14.7)
Body mass index, kg/m^2		
Baseline	207	25.7 (4.6)
First scan	209	27.0 (5.3)
Waist circumference, cm		
Baseline	203	77.0 (11.3)
First scan	208	81.8 (12.4)
Systolic blood pressure, mm Hg		
Baseline	205	106.6 (11.6)
First scan	209	118.0 (15.2)
Current smoking, yes, %		
Baseline	45	21.6
First scan	29	14.0
Alcohol, g/day		
Baseline	203	15.0 (14.6)
First scan	207	4.4 (6.6)
Physical activity, kcal/day		
Baseline	203	1687.4 (1620.2)
First scan	199	1962.7 (1445.6)
Hormone replacement therapy, yes, %		
Baseline	16	7.7
First scan	99	47.4
Trait anger		
Baseline	203	17.9 (4.3)
First scan	207	17.4 (4.0)

Note. Study entry is 7.4 years (SD = 0.9, range=4.2 to 10.8) before the first carotid scans.

Anger and progression, women were categorized into quartiles based on the sample distribution of Trait Anger scores. Figure 1 presents the percent increase in IMT according to these categories. Women scoring in the lowest quartile of Trait Anger scores showed the least progression of atherosclerosis over 3 years when compared with women who scored at or above the second quartile on Trait Anger (percentage change in mean IMT: M = 1.96, SE = 1.18 vs. M = 5.66, SE = 0.61, $F(5,197) = 7.8$, $p < .006$).

None of the significant results changed substantially with inclusion of behavioral and biological covariates. Anger In and Cook-Medley hostile attitudes were not associated with progression of carotid atherosclerosis (p's $> .45$; data not shown).

Metabolic Syndrome as a Possible Mediator of Trait Anger and Progression of IMT

Baseline Trait Anger scores tended to predict the risk for developing the metabolic syndrome up to the first carotid scans (b = 3.8, $p < .09$ in logistic regression analysis), and predicted significantly the risk of developing the metabolic syndrome to the second carotid scans (b = 4.2, $p < .05$ in logistic regression analysis). A priori hypothesized path model involving direct and indirect paths via the metabolic syndrome was tested. The model showed an adequate fit. Trait Anger scores significantly predicted a greater risk for developing the metabolic syndrome up to the second carotid scans. The risk for developing the metabolic syndrome, in turn, was significantly associated with an increase in mean IMT. Trait Anger scores did not directly predict the progression of carotid atherosclerosis (Figure 2).

Finally, we tested the two anger dimensions measured at baseline, in relation to progression of carotid atherosclerosis. Angry reaction predicted the progression of carotid atherosclerosis (mean IMT: $\beta = 0.17$, $t = 2.75$, $p < .006$; maximum IMT: $p < .46$), whereas angry temperament was not associated with carotid atherosclerosis progression (p's $> .64$).

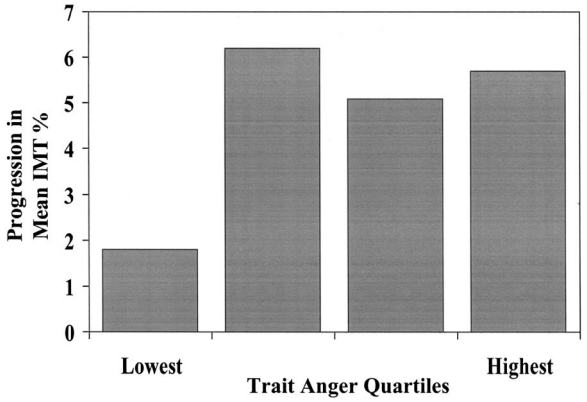

Figure 1. Percent increase in mean IMT over 3 years according to quartiles of baseline Trait Anger scores measured 7.4 years before the first scan. ($F(7,195) = 2.68$, $p < .05$ in ANCOVA, controlling for mean IMT measured at first carotid scans, age at the time of Trait Anger measure and length of follow-up; $p < .05$ for linear trend.)

DISCUSSION

The present study tested whether women who score high in Trait Anger, Anger In, and hostile attitudes scales experience progression of carotid atherosclerosis in a sample of healthy women followed throughout the perimenopausal and postmenopausal years. The present study also tested whether the metabolic syndrome mediated any potential associations between the emotional and cognitive components of hostility and carotid atherosclerosis. Consistent with the study hypotheses, women who experienced more intense and frequent feelings of anger predicted progression of carotid atherosclerosis over 3 years. Analyses with the subscales of the Spielberger Trait Anger scale suggested that this was particularly true for those women who scored high on the Angry Reaction subscale. Longitudinal associations between intense and frequent feelings of anger and progression of carotid atherosclerosis predicted the risk for developing the metabolic syndrome over the follow-up, the risk for developing the metabolic syndrome, in turn, predicting progression of carotid atherosclerosis. These results, thus, suggest that psychologically vulnerable women ought to be targets of risk reduction programs early in the natural history of atherosclerosis. Early intervention focusing on anger management may prove to be helpful in primary prevention of CHD. In addition to treatment of anger, the added value of psychological intervention, and anger management in particular, to risk reduction programs aiming at lifestyle changes or treatment of established CHD risk factors ought to be considered.

Of interest is that our data indicate that only women in the lowest quartile of anger scores experienced low levels of progression. Stated differently, once over a threshold of anger, women in the highest three quartiles of anger scores appeared to have similar risk. This result suggests that intervention ought not to focus on groups exhibiting the extreme characteristics, but the intervention and management of anger may be beneficial for women reporting less often and mildly elevated levels of angry feelings.

In a larger sample that included the same women as in the present analysis, Anger In and Cook-Medley hostile attitudes scores measured 10 to 1.5 years earlier predicted the extent of IMT at the first carotid scan (15). The current results showed that Anger In and Cook-Medley hostile attitudes were not associated with progression of carotid atherosclerosis, perhaps due to a smaller sample. On the other hand, this null result on progression supports the suggestion that some components of hostility may be more harmful than others (1,4). The meta-analyses by Miller et al. (1) suggested that Cook-Medley hostile attitudes might play a more crucial role in predicting all-cause mortality than predicting CHD morbidity or mortality.

The atherosclerotic process involves multiple biochemical, immune-inflammatory, and hemodynamic processes in combination with various other factors (30). In addition to the metabolic syndrome, other risk factors and physiological processes may act as mediators or underlie the current associa-

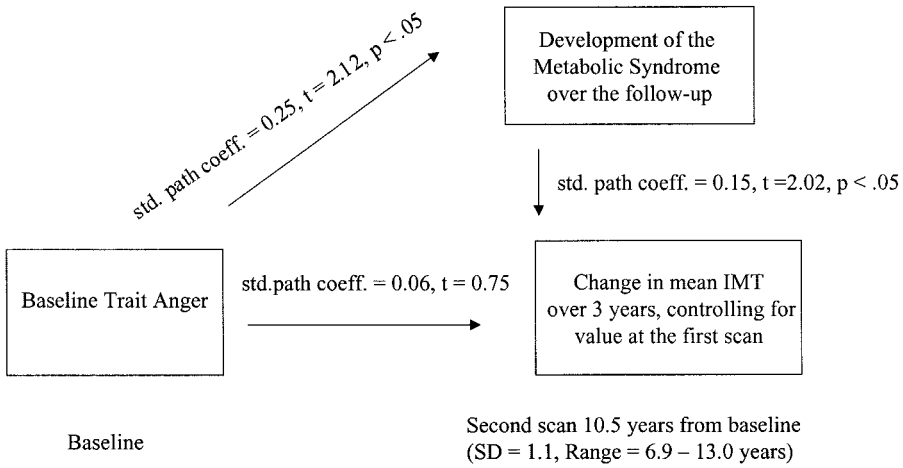

Figure 2. A path model showing associations among Trait Anger, metabolic syndrome and progression of carotid atherosclerosis. The model included age at the time of Trait Anger measure, duration between baseline and to the first carotid scans, and duration between the first and second carotid scans. These paths are not shown for the clarity of figure. The metabolic syndrome variable 0 = remained free from the metabolic syndrome over the follow-up, 1 = developed the metabolic syndrome over the follow-up. Continuous variables were log-transformed. χ^2 (3) = 6.027, p = .1096, CFI = 0.94, RMSEA = 0.074.

tions. Prior studies have demonstrated that anger may produce coronary vasoconstriction in previously narrowed coronary arteries in patients with symptomatic ischemia (31). Facial expressions of anger were more common in male patients with coronary artery disease exhibiting myocardial ischemia (wall motion abnormality and left ventricular ejection fraction) during Type A Structured Interview than were patients with no ischemia (32). Other autonomic nervous system (33), neuroendocrine (34,35) and immune-inflammatory (35) mechanisms relating to negative emotions may be involved as well. In the current study, we found no evidence that behavioral lifestyle factors explained the significant findings. This may reflect the health of the sample: smoking and alcohol consumption on average decreased, while physical activity increased over time (see Table 2), and almost 50% of the sample was on hormone replacement therapy at the time of the first carotid scans. On the other hand, the behavioral lifestyle factors and the metabolic syndrome constituents are correlated. Owens et al. (36) have demonstrated in the HWS that changes in physical activity and changes in obesity, lipids, and blood pressure occur concurrently over time. Finally, the current associations may reflect a common, underlying genetic predisposition to CHD, involving risk factors and disease processes. Clearly, all possible additional pathways and predisposing factors need further, intense examination.

Limitations of the study include that our findings can only be generalized to women, primarily of Caucasian background. Strengths of the study include repeat assessments of both psychological and carotid disease factors, and a high quality assessment of carotid disease.

To summarize, the current study shows that Trait Anger predicts progression of carotid atherosclerosis across 3 years in middle-aged women, and that this association may be mediated via the metabolic syndrome. Mechanisms of the relationships among psychological and biological factors deserve further examination.

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