ORIGINAL RESEARCH

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Hostility, Health Behaviors, and Risk of Recurrent Events in Patients With Stable Coronary Heart Disease: Findings From the Heart and Soul Study

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***Background*—**Hostility is a significant predictor of mortality and cardiovascular events in patients with coronary heart disease (CHD), but the mechanisms that explain this association are not well understood. The purpose of this study was to evaluate potential mechanisms of association between hostility and adverse cardiovascular outcomes.

***Methods and Results*—**We prospectively examined the association between self-reported hostility and secondary events (myocardial infarction, heart failure, stroke, transient ischemic attack, and death) in 1022 outpatients with stable CHD from the Heart and Soul Study. Baseline hostility was assessed using the 8-item Cynical Distrust scale. Cox proportional hazard models were used to determine the extent to which candidate biological and behavioral mediators changed the strength of association between hostility and secondary events. During an average follow-up time of 7.4±2.7 years, the age-adjusted annual rate of secondary events was 9.5% among subjects in the highest quartile of hostility and 5.7% among subjects in the lowest quartile (age-adjusted hazard ratio [HR]: 1.68, 95% confidence interval [CI]: 1.30 to 2.17; $P<0.0001$). After adjustment for cardiovascular risk factors, participants with hostility scores in the highest quartile had a 58% greater risk of secondary events than those in the lowest quartile (HR: 1.58, 95% CI: 1.19 to 2.09; $P=0.001$). This association was mildly attenuated after adjustment for C-reactive protein (HR: 1.41, 95% CI, 1.06 to 1.87; $P=0.02$) and no longer significant after further adjustment for smoking and physical inactivity (HR: 1.25, 95% CI: 0.94 to 1.67; $P=0.13$).

***Conclusions*—**Hostility was a significant predictor of secondary events in this sample of outpatients with baseline stable CHD. Much of this association was moderated by poor health behaviors, specifically physical inactivity and smoking. **(*J Am Heart Assoc.* 2013;2:e000052 doi: 10.1161/JAHA.113.000052)**

Key Words: coronary artery disease • epidemiology • hostility • mortality • observational studies

Seminal work by cardiologists Friedman and Rosenman over 50 years ago showed that patients who exhibited the "Type A behavior pattern," characterized by competitiveness, excessive drive, and an enhanced sense of time urgency, had more risk factors for coronary heart disease (CHD) and were more likely to suffer from major adverse cardiovascular (CV) events than patients without the Type A behavior pattern.[1–4] Subsequent research focused on anger and hostility as the aspects of the Type A behavior that were particularly cardiotoxic.[5–7] Since then, 12 prospective observational studies have demonstrated that anger and hostility are associated with an increased risk of both incident CHD and recurrent CV events.[8]

Although the link between hostility and CV events has been reproducibly shown, the mechanisms that explain this association are not well understood. One possibility is that hostility may exert a cardiotoxic effect through a physiologic pathway.[9–11] Greater adrenergic responses to stressful psychological stimuli can increase blood pressure,[12–14] coronary vasoconstriction,[15] inflammation,[16] and activation of platelets.[17,18] A triggering event, such as an outburst of anger, may increase the risk of nonfatal myocardial infarction (MI) or CHD death.[19] Another possibility is that hostility may promote poor health behaviors such as smoking, physical inactivity, and medication nonadherence, which increase the risk of CV events.[20–22]

In a prospective cohort study of 1022 patients with stable CHD, we sought to evaluate the association of hostility with potential biological and behavioral factors that may increase

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An accompanying Table S1 is available at http://jaha.ahajournals.org/content/2/5/e000052/suppl/DC1

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the risk of secondary events, and to determine the extent to which each of these potential factors might explain the relation between hostility and adverse CV outcomes.

Methods

We evaluated participants from the Heart and Soul Study, a prospective cohort study that was designed to determine how psychological factors influence the outcomes of patients with stable CHD. A detailed description of the recruitment process from the Heart and Soul Study has been previously described.[23] Between September 2000 and December 2002, 1024 patients with stable CHD were enrolled, including 240 from public health clinics in the Community Health Network of San Francisco, 346 from the University of California San Francisco Medical Center, and 438 from the San Francisco or Palo Alto VA Medical Centers. Of these 1024, 2 were lost to follow-up, leaving 1022 for this analysis. Study participants completed a daylong baseline study appointment that included a medical history interview, a physical examination, an exercise treadmill test with stress echocardiography, a comprehensive health status questionnaire, and a fasting blood draw. Participants were also provided a 3 L collection jug and instructed to save all urine between the end of their baseline appointment and the time when the researcher recovered their urine. Our protocol was approved by the following institutional review boards: the Committee on Human Research at University of California, San Francisco; the Medical Human Subjects Committee at Stanford University; the Human Subjects Committee at the Veterans Affairs Palo Alto Health Care System; and the Data Governance Board of the Community Health Network of San Francisco. All participants provided written informed consent.

Hostility

At baseline, we administered the 8-item "Cynical Distrust" scale (Table 1), which was originally derived from the Cook-Medley hostility subscale of the Minnesota Multiphasic Personality Inventory[24,25] and found to predict progression of atherosclerosis.[26] The 8-item Cynical Distrust scale has previously been validated and shown to predict CV events. Among 2125 men who completed the 8-item Cynical Distrust scale as part of the Kuopio Ischemic Heart Disease Risk Factor Study, those with scores in the top quartile had more than twice the risk of MI and CV death as compared with those who had scores in the lowest quartile.[27] In the present study, we created an imputed score for participants who did not answer all 8 questions but answered at least 75% of questions. This score was calculated by dividing the number of positive responses over the total number of questions answered.

Table 1. Eight-Item Cynical Distrust Scale

Read each statement and decide whether it is true or false as applied to you	
1.	I think most people would lie to get ahead
2.	Most people are honest chiefly through fear of getting caught
3.	Most people will use somewhat unfair means to gain profit or an advantage rather than to lose it
4.	No one cares much what happens to you
5.	It is safer to trust nobody
6.	Most people make friends because friends are likely to be useful to them
7.	Most people inwardly dislike putting themselves out to help other people
8.	I commonly wonder what hidden reason another person may have for doing something nice to me

Other Patient Characteristics

Age, sex, race, education, and medical history were determined by self-report. The presence of major depressive disorder was determined using the Computerized Diagnostic Interview Schedule for the DSM-IV (C DIS-IV). If study participants were found to have a major depressive disorder within the past month, they were instructed to discuss their symptoms with their primary care physician and were provided a list of local resources. We used the Hospital Anxiety and Depressions Scale (HADS)[28] to measure anxiety. We measured height and weight and calculated body mass index in kg/m^2. Participants were instructed to bring their medication bottles to the study appointment, and study personnel recorded all current medications. We also measured many CV risk factors. Left ventricular ejection fraction was obtained by echocardiography using an Acuson Sequoia Ultrasound System with a 3.5-MHz transducer. Participants also completed an exercise treadmill test using the standard Bruce protocol at the baseline examination. We used the total number of metabolic equivalents tasks achieved to measure exercise capacity. We defined inducible ischemia as the presence of wall motion abnormalities at peak exercise that were not present at rest. Low- and high-density lipoprotein levels were obtained from venous blood after an overnight fast. Systolic and diastolic blood pressure were measured in the supine position after 5 minutes of rest.

Potential Biological Mediators

Biological factors measured at baseline were 24-hour heart rate variability, 24-hour urinary norepinephrine, 24-hour urinary cortisol, C-reactive protein, whole blood serotonin, and omega 3 fatty acid levels. Three-channel 24-hour ambulatory Holter electrocardiography was used to assess

heart rate variability, including the natural log of very low frequency power. Twenty-four–hour urine samples were collected to measure norepinephrine and cortisol excretion. Norepinephrine was measured using gas chromatography/mass spectrometry at the Associated Regional and University Pathologists, Inc. Cortisol was analyzed using either a radioimmunoassay or high performance liquid chromatography/tandem mass spectrometry. Whole blood serotonin levels were determined using high-pressure liquid chromatography. High-sensitivity C-reactive protein was measured using either the Roche Integra assay or the Beckman Extended Range assay. Blood levels of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) were measured by capillary gas chromatography as the percentage composition of total fatty acid methyl esters in the red blood cell membranes.

Potential Behavioral Mediators

Behavioral factors measured at baseline included smoking, alcohol, medication adherence, and physical activity. Smoking was assessed by self-report questionnaire. Alcohol use was assessed with the AUDIT-C, a validated 3-question screening questionnaire that assesses frequency and quantity.[29] Regular alcohol use was defined as a score of ≥4 (range 0 to 12), which indicates a positive screen for alcohol dependence. Medication adherence was assessed using the question, "In the past month, how often did you take your medications as the doctor prescribed?" and possible responses included: "all of the time (100%)", "nearly all of the time (≈90%)", "most of the time (≈75%)", "about half of the time (≈50%)", and "less than half of the time (<50%)". Medication nonadherence was defined as "most of the time (≈75%)" or less.[30] Physical activity was assessed by the question, "Which of the following statements best describes how physically active you have been during the last month, that is, done activities such as 15 to 20 minutes of brisk walking, swimming, general conditioning, or recreational sports?" and possible responses included: "not at all active (0 times per month)", "a little active (1 to 2 times per month)", "fairly active (3 to 4 times per month)", "quite active (1 to 2 times per week)", "very active (3 to 4 times per week)", and "extremely active (>5 times per week)". Physical inactivity was defined as not at all or a little (versus fairly, quite, very or extremely) active.[31] Single-response items assessing self-reported physical activity have previously demonstrated excellent construct validity.[32,33]

Secondary Events

The primary outcome variable (secondary events) was defined as time-to-first-MI, heart failure, stroke/transient ischemic attack (TIA), or death. Events were also analyzed separately. Following the baseline assessment, study participants (or their proxy) were contacted annually by telephone, and were asked about hospitalization for "heart trouble". Participants were specifically asked about heart attack or MI, coronary artery bypass surgery, coronary angioplasty, angina requiring admission to a hospital, congestive heart failure requiring admission to a hospital, stroke, and other hospitalizations. For any reported event, medical records, electrocardiograms, death certificates, and coroner's reports were retrieved and reviewed by 2 independent blinded adjudicators. If the adjudicators agreed, their classification was binding. If the adjudicators disagreed, they reconsidered their classification and requested consultation from a third blinded adjudicator if needed. Heart failure was defined as hospitalization involving at least 2 of the following signs and symptoms: paroxysmal nocturnal dyspnea, orthopnea, elevated jugular venous pressure, pulmonary rales, third heart sound, and cardiomegaly or pulmonary edema on chest x-ray. MI was defined using standard criteria.[34] Stroke was defined as a new neurological deficit not known to be secondary to brain trauma, tumor, infection, or other cause. TIA was defined as a focal neurological deficit lasting >30 seconds but no longer than 24 hours, with rapid evolution of symptoms to the maximal level of deficit in <5 minutes and with subsequent complete resolution. Death was confirmed by death certificates and coroner's reports.

Statistical Analyses

The goal of this study was to evaluate the mechanisms of association between hostility and secondary events in patients with stable CHD by measuring the extent to which adjustment for potential biological and behavioral factors attenuated the strength of association. Baseline characteristics were compared across hostility quartiles using 1-way analysis of variance (ANOVA) for continuous variables and chi square test for dichotomous variables. The association of hostility with secondary events was estimated using Cox proportional hazard models, with hostility entered both as a continuous variable (per standard deviation increase) and as a categorical variable (quartiles). Covariates considered in this analysis included demographic variables, comorbid conditions, CV risk factors, and potential behavioral and biological factors. We tested the proportional hazard assumption with our multivariate models and found no evidence of contradiction.

The role of each covariate in the association between hostility and secondary events was assessed using a 3-step framework for formal mediation analysis.[35] The 3 steps were: (1) assess if hostility is associated with secondary events; (2) assess if hostility is associated with the potential mediator; (3) assess if the strength of the association between hostility

and secondary events was attenuated after adjusting for the covariate. For step 3, we determined the extent to which each covariate changed the strength of association between hostility and secondary events. The percentage change in the effect size (age-adjusted log hazard ratio [HR]) for hostility (quartile IV versus I) was calculated after adjustment for each covariate. If the change in effect size was >5%, the covariate was considered a potential confounder or mediator and included in subsequent multivariable analyses. To confirm these results, we also estimated the strength of mediation using the Sobel-Goodman test.[36]

The presence of major depression did not meet our a priori definition for potential mediation; however, we included this covariate in multivariate analyses because we thought it would more accurately assess whether the association between hostility and secondary events was independent of depression. We used Wald tests to check for interactions of hostility with age, sex, and race in age-adjusted and multivariable-adjusted models. All analyses were performed using SAS version 9.0 (SAS Institute Inc) and STATA version 12.0 (StataCorp).

Results

A total of 1022 predominately male participants were followed for an average of 7.4±2.7 years. The distribution of hostility scores is shown in Figure 1. As compared to participants with low hostility scores, those with high hostility scores were younger, less likely to be white, and less likely to have graduated from high school (Table 2). They were also more likely to have hypertension, diabetes, anxiety symptoms, and depressive symptoms. Notably, participants with high hostility scores had increased levels of both norepinephrine (P=0.02) and C-reactive protein (P=0.008) compared to those with low hostility scores. They were also more likely to smoke, less likely to take medications as prescribed, less physically active, and had a reduced exercised capacity (all P values <0.001).

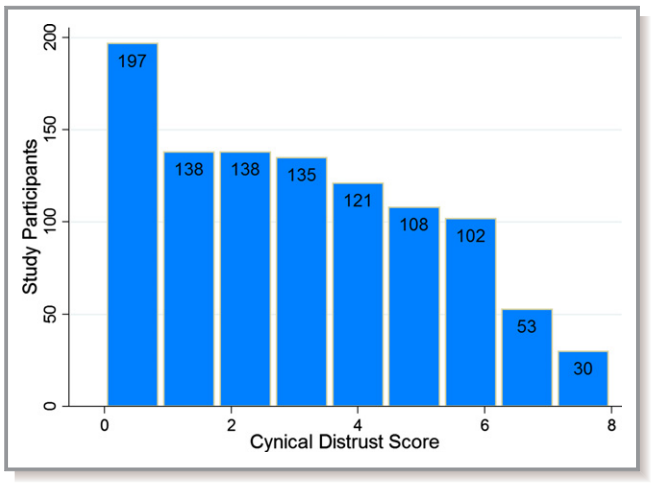

Figure 1. Distribution of cynical distrust scores. Distribution of self-reported 8-item cynical distrust scores administered at baseline. All items were true/false questions and true responses were worth 1 point. Cynical distrust scores ranged from 0 to 8. Approximately 99% of study participants (1011/1022) answered all 8 items.

A total of 490 participants experienced 1 or more secondary events in 6581 person-years of follow-up. Overall, the age-adjusted annual rate of CV events or death was 9.5% among patients who had hostility scores in the highest quartile and 5.7% in those with hostility scores in the lowest quartile (Figure 2). As compared with participants in the lowest quartile, those with hostility scores in the highest quartile had a 49% greater risk of CV events (age-adjusted HR: 1.49, 95% confidence interval [CI]: 1.07 to 2.09) and a 50% greater risk of death (HR 1.50, 95% CI, 1.12 to 2.00) (Table 3). No statistically significant association was detected between hostility quartiles and heart failure (HR 1.22, 95% CI, 0.79 to 1.88), MI (HR 1.31, 95% CI, 0.78 to 2.21) or stroke/TIA (HR 1.42, 95% CI, 0.73 to 2.74), but all of the point estimates of the HRs were in the expected direction. When entered as a continuous variable, each standard-deviation (2.3 point) increase in hostility score was associated with a 17% increased risk of CV events (HR 1.17, 95% CI, 1.05 to 1.32) and an 18% greater risk of death (HR 1.18, 95% CI, 1.07 to 1.30).

Several variables met the criteria for potential confounding or mediation (changed the effect size for hostility by 5% or more). These variables included (in descending order of magnitude) physical inactivity, diabetes mellitus, current smoking, log C-reactive protein, white race, current antidepressant use, history of congestive heart failure, and left ventricular ejection fraction (Figure 3, Table S1). Notable variables that did not meet the criterion for confounding or mediation included male sex, history of MI, lipid levels, and norepinephrine excretion. We also analyzed each potential biological and behavioral mediator with the Sobel-Goodman test for mediation. The test confirmed that log C-reactive protein, current smoking, and physical inactivity each explained >10% of the effect for the association between hostility and recurrent events (all P values <0.15).

After adjustment for demographics, comorbid conditions, CV risk factors, and antidepressant use, those with hostility scores in the highest quartile had a 58% greater rate of secondary events than those in the lowest quartile (HR: 1.58, 95% CI: 1.19 to 2.09; P=0.001) (Table 4), and each standard deviation increase in hostility remained associated with a 18% greater risk of secondary events (HR: 1.18, 95% CI: 1.07 to 1.30; P=0.001) (Table 5). This association was slightly attenuated after adjustment for potential biological mediators and further adjustment for behavioral factors (smoking and physical inactivity) attenuated the association between

Table 2. Baseline Characteristics of 1022 Participants With Coronary Heart Disease, by Quartile of Hostility

Variable*	Hostility Quartile				*P* Value
	I (<1.1), n=333	II (1.1 to 3.0), n=272	III (3.1 to 5), n=232	IV (>5), n=185	
Demographic Characteristics					
Age, y	67.5±10.8	67.1±11.0	67.4±10.6	64.5±10.8	0.01
Male sex	266 (80%)	223 (82%)	194 (84%)	155 (84%)	0.61
High school graduate	316 (95%)	245 (90%)	185 (80%)	144 (78%)	<0.0001
Body mass index, kg/m^2	27.8±5.0	28.6±5.3	28.7±5.8	28.8±5.4	0.06
Ethnicity					
White	247 (74%)	169 (62%)	116 (50%)	83 (45%)	<0.0001
Black	28 (8%)	49 (18%)	44 (19%)	46 (25%)	<0.0001
Asian	26 (8%)	26 (10%)	33 (14%)	32 (17%)	0.004
Hispanic	26 (8%)	17 (6%)	27 (12%)	19 (10%)	0.14
Comorbid Conditions					
Hypertension	224 (67%)	184 (68%)	173 (75%)	141 (77%)	0.04
Myocardial infarction	173 (52%)	150 (56%)	123 (53%)	101 (55%)	0.85
Stroke	41 (12%)	40 (15%)	40 (17%)	26 (14%)	0.42
Heart Failure	58 (18%)	41 (15%)	42 (18%)	38 (21%)	0.50
Diabetes mellitus	63 (19%)	71 (26%)	65 (28%)	66 (36%)	0.0003
Depression[†]	55 (17%)	54 (20%)	50 (22%)	64 (35%)	<0.0001
Anxiety[‡]	4.48±3.55	4.98±3.46	5.89±3.94	7.22±4.52	<0.0001
Cardiovascular Risk Factors					
Left ventricular ejection fraction, %	62.0±9.5	62.0±9.5	60.8±10.5	61.7±8.9	0.51
Low-density lipoprotein, mg/dL	104.3±32.0	103.0±34.4	103.7±36.1	107.1±32.8	0.63
High-density lipoprotein, mg/dL	47.2±14.4	46.0±15.5	44.3±13.0	45.2±12.4	0.10
Systolic blood pressure, mm Hg	131±19	133±20	135±24	134±21	0.12
Diastolic blood pressure, mm Hg	74±11	74±11	76±13	76±11	0.07
Inducible ischemia	82 (26%)	54 (21%)	53 (25%)	39 (24%)	0.59
Medication Use					
Aspirin	262 (79%)	208 (76%)	175 (75%)	147 (79%)	0.70
Statin	215 (65%)	181 (67%)	142 (61%)	118 (64%)	0.66
Renin-angiotensin system inhibitor	164 (49%)	137 (50%)	122 (53%)	101 (55%)	0.66
β-blocker	190 (57%)	162 (60%)	130 (56%)	110 (59%)	0.82
Any antidepressant	44 (13%)	52 (19%)	42 (18%)	49 (26%)	0.003
Potential Biological Mediators					
Heart rate variability, lnVLF, ms^2	6.4±0.9	6.3±0.9	6.3±0.7	6.1±0.8	0.20
Serotonin[§], ng/mL	115±73	109±97	115±69	115±79	0.79
Cortisol, μg/d	40.7±35.8	39.3±24.4	36.2±27.3	36.4±25.1	0.29
Norepinephrine, μg/d	50.1±22.9	52.5±27.4	48.9±28.6	56.7±28.2	0.02
Log C-reactive protein, mg/L	0.5±1.4	0.8±1.3	0.8±1.2	0.8±1.2	0.008
Omega-3 fatty acids, % DHA+EPA	4.2±2.0	4.3±2.0	4.1±2.1	4.0±2.2	0.41

Continued

Table 2. Continued

Variable*	Hostility Quartile				*P* Value
	I (<1.1), n=333	II (1.1 to 3.0), n=272	III (3.1 to 5), n=232	IV (>5), n=185	
Potential Behavioral Mediators					
Regular alcohol use	102 (31%)	86 (32%)	64 (28%)	41 (22%)	0.13
Current smoking	42 (13%)	50 (18%)	48 (21%)	61 (33%)	<0.0001
Medication nonadherence	12 (4%)	27 (10%)	18 (8%)	26 (14%)	0.0003
Physical activity					
Not at all active	45 (14%)	46 (17%)	42 (18%)	55 (30%)	<0.0001
A little active, 1 to 2 times/month	40 (12%)	53 (19%)	48 (21%)	41 (22%)	
Fairly active, 3 to 4 times/month	43 (13%)	42 (15%)	38 (16%)	33 (18%)	
Quite active, 1 to 2 times/week	57 (17%)	40 (15%)	38 (16%)	20 (11%)	
Very active, 3 to 4 times/week	94 (28%)	63 (23%)	43 (19%)	19 (10%)	
Extremely active, ≥5 times/week	53 (16%)	28 (10%)	23 (10%)	15 (8%)	
Exercise capacity, MET	8.1±3.5	7.2±3.4	6.6±3.0	6.8±3.1	<0.0001

DHA indicates docosahexaenoic acid; EPA, eicosapentaenoic acid; lnVLF, natural log of very low frequency; MET, metabolic equivalent tasks; SD, standard deviation.
*Values are mean±SD for continuous variables and number (%) for dichotomous variables.
†Participants with current depression as ascertained by the Computerized Diagnostic Interview Schedule for the DSM-IV (C DIS-IV).
‡Anxiety was measured using the Hospital Anxiety and Depression Scale (HADS-A).
§Serotonin measured only among those who were not currently taking selective serotonin reuptake inhibitors (SSRIs).

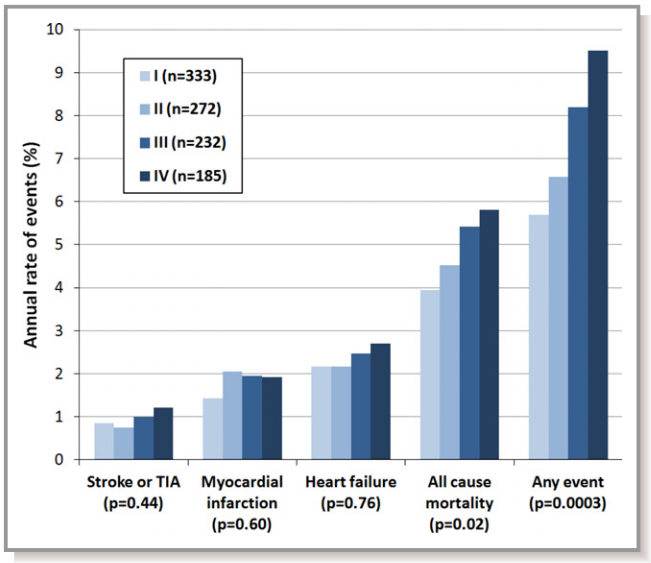

Figure 2. Age-adjusted annual rate of secondary events by hostility quartile. Quartile I (lightest shade of blue) represents the lowest self-reported cynical hostility scores, with each sequential quartile increasing in hostility severity. Increasing hostility was significantly associated with "All-cause mortality" and "Any event", a composite of stroke/transient ischemic event, myocardial infarction, heart failure, and death. TIA indicates transient ischemic attack.

hostility and secondary events. In the final fully adjusted models, which included adjustment for all potential confounding and mediating variables, hostility was no longer predictive of adverse outcomes (Tables 4 and 5). We also substituted exercise capacity for self-reported physical activity and found a similar reduction in the effect size for hostility when entered as highest versus lowest quartile (HR: 1.24, 95% CI: 0.92 to 1.69; *P*=0.16) and as each standard deviation increase (HR: 1.09, 95% CI: 0.98 to 1.21; *P*=0.13). We found no evidence that the effect of hostility on secondary events differed by age, sex, or race (all *P* values for interaction >0.1).

Discussion

In a prospective cohort of over 1000 outpatients with preexisting CHD, we found that individuals with baseline hostility scores in the highest quartile had a 50% greater risk of mortality, and a 49% greater risk of CV events (MI, heart failure, stroke or TIA) than those with hostility scores in the lowest quartile. Adjustment for potential biological factors somewhat attenuated the association between hostility and recurrent CV events. However, the association was no longer significant after adjustment for behavioral factors (physical activity and current smoking). These findings suggest that the association between hostility and recurrent CV events may be largely attributable to poor health behaviors.

Previous studies have suggested that poor health behaviors may contribute to the association between hostility and secondary events in patients with stable CHD.[8,27] Everson and colleagues[27] examined the association between cynical hostility and risk of mortality and incident MI in 2125 male subjects between 42 and 60 years of age and concluded that

Table 3. Annual Rates of Secondary Events During a Mean of 7.4±2.7 Years of Follow-up, by Baseline Hostility Score

Event	Number of Events (Age-Adjusted Annual Rate)		Hostility (Quartile IV vs I*)		Hostility (per SD† Increase)	
	Hostility Quartile IV	Hostility Quartile I	Age-Adjusted HR (95% CI)	*P* Value	Age-Adjusted HR (95% CI)	*P* Value
Cardiovascular Events	59 (5.42%)	87 (3.55%)	1.49 (1.07 to 2.09)	0.02	1.17 (1.05 to 1.32)	0.007
Heart failure	33 (2.70%)	58 (2.17%)	1.22 (0.79 to 1.88)	0.36	1.07 (0.92 to 1.24)	0.38
Myocardial infarction	23 (1.92%)	37 (1.43%)	1.31 (0.78 to 2.21)	0.32	1.12 (0.94 to 1.33)	0.20
Stroke or TIA	15 (1.21%)	22 (0.85%)	1.42 (0.73 to 2.74)	0.30	1.15 (0.91 to 1.45)	0.26
All-cause mortality	77 (5.81%)	113 (3.94%)	1.50 (1.12 to 2.00)	0.007	1.18 (1.07 to 1.30)	0.001
Any of above outcomes	103 (9.51%)	139 (5.69%)	1.68 (1.30 to 2.17)	<0.0001	1.22 (1.12 to 1.33)	<0.0001

CI indicates confidence interval; HR, hazard ratio; SD, standard deviation; TIA, transient ischemic attack.
*Hostility quartile IV (n=185) includes study participants who scored the highest on the 8-item cynical distrust scale. Hostility quartile I (n=333) includes study participants who scored the lowest.
†The standard deviation of hostility (8-item Cynical Distrust scale) is 2.3 points.

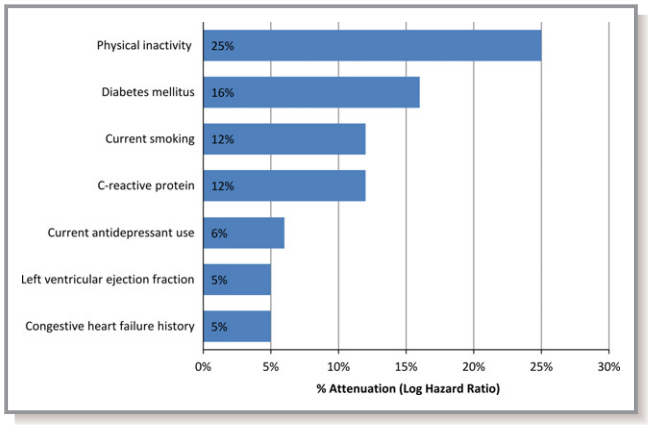

Figure 3. Change in strength of association between hostility (quartile IV vs I) and secondary events after adjustment for potential confounders and mediators. The change in effect size is expressed as the percent change of the age-adjusted log hazard ratio (β-coefficient). Covariates that changed the effect size for hostility by <5% included: male sex, high school graduate, body mass index, hypertension, history of myocardial infarction, history of stroke/transient ischemic attack, history of revascularization, current depression (C DIS-IV), low-density lipoprotein, aspirin use, β-blocker use, ACE/ARB use, statin use, heart rate variability, serotonin levels (among non-SSRI users), cortisol levels, norepinephrine levels, omega-3 fatty acid levels, alcohol use (AUDIT-C score), and medication nonadherence. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; C DSI-IV, Computerized Diagnostic Interview Schedule for the DSM-IV; SSRI, selective serotonin reuptake inhibitors.

the association between hostility and increased risk of death and incident MI were mediated primarily through behavioral risk factors. However, this study and others have not simultaneously adjusted for depression, which is highly correlated with hostility[37–39] and whose association with secondary events is likewise mediated by health behaviors.[31,40,41] Our study adds to this literature by demonstrating that health behaviors mediate the association of hostility and secondary events independent of depression. In addition, our findings expand upon prior work by also examining potential biological factors (heart rate variability, norepinephrine, cortisol, C-reactive protein, omega 3 fatty acids, and serotonin). We found biological factors accounted for much less of this association than health behaviors. Although patients with hostility had higher levels of norepinephrine and C-reactive protein, adjusting for these factors only minimally reduced the strength of association between hostility and adverse events. These findings suggest that the association of hostility with potential biological factors, such as C-reactive protein and norepinephrine, may also be mediated by health behaviors.

A quantitative analysis by Bunde and Suls[42] in 2006 examined the relationship between the Cook-Medley hostility scale and traditional CHD risk factors, including smoking and physical activity. Although their findings were limited by a lack of prospective evidence, they conclude that baseline hostility is significantly associated with smoking but not physical activity in cross-sectional studies. However, the variability of measurement of physical activity was significant across studies. Interestingly, hostility was found to be associated with surrogates of physical activity, including body mass index and waist-to-hip ratio.

Another reason why biological factors may have contributed less than health behaviors to the association between hostility and secondary events is that hostility may exert other cardiotoxic physiologic effects that were not measured in this study. It has been suggested that acute anger outbursts may lead to hemodynamic stresses that can result in coronary occlusion and MI in the presence of vulnerable atherosclerotic plaque.[19,43–45] Thus, an acute trigger event may predispose hostile patients to myocardial ischemia and ventricular arrhythmias. However, recent evidence casts doubt about autonomic nervous system dysregulation as a contributing

Table 4. Association Between Baseline Hostility (Entered Quartile IV vs I) and Secondary Events, With Adjustment for Potential Biological and Behavioral Factors

	All-Cause Mortality		Cardiovascular Events*		Any Event	
Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1 (adjusted for age)	1.50 (1.12 to 2.00)	0.007	1.49 (1.07 to 2.08)	0.02	1.68 (1.30 to 2.17)	<0.0001
Model 2 (adjusted for potential confounding variables)	1.48 (1.08 to 2.02)	0.02	1.40 (0.97 to 2.01)	0.07	1.58 (1.19 to 2.09)	0.001
Model 3 (add biological factors)	1.37 (1.00 to 1.88)	0.05	1.22 (0.84 to 1.77)	0.29	1.41 (1.06 to 1.87)	0.02
Model 4 (add behavioral factors)	1.20 (0.86 to 1.66)	0.28	1.20 (0.84 to 1.78)	0.30	1.34 (1.00 to 1.78)	0.05
Model 5 (add both biological and behavioral factors)	1.16 (0.84 to 1.61)	0.38	1.13 (0.77 to 1.65)	0.53	1.25 (0.94 to 1.67)	0.13

Model 1=adjusted for age. Model 2=adjusted for age, sex, race, diabetes mellitus, congestive heart failure, antidepressant use, anxiety (HADS-A), depression (C DIS-IV), and LVEF. Model 3=adjusted for all variables in Model 2 plus log C-reactive protein (this was the only biological mediator that resulted in a >5% change in the effect size for hostility). Model 4=adjusted for all variables in Model 2 plus current smoking and physical inactivity. Model 5=adjusted for all variables in Model 2 plus log C-reactive protein, current smoking, and physical inactivity. C DIS-IV indicates Computerized Diagnostic Interview Schedule for the DSM-IV; CI, confidence interval; HADS-A, Hospital Anxiety and Depression Scale; HR, hazard ratio; LVEF, left ventricular ejection fraction.

*Cardiovascular events include stroke, transient ischemic attack, myocardial infarction, and heart failure.

mechanism underlying the hostility-CHD relationship. Sloan et al[46] randomized participants to 12 weeks of cognitive behavior therapy or a wait-list control and found that a reduction in hostility was not accompanied by a significant change in heart rate variability. Consistent with this negative finding, we found that 24-hour norepinephrine excretion (an indicator of sympathetic activity over time[47,48]) is associated with hostility but does not explain the association between hostility and secondary events.

We also found that the effect of hostility on secondary events did not differ by age, sex, or race. In contrast, Boyle et al[49] reported that hostility was significantly associated with an increased risk of total mortality in younger but not older patients suspected for coronary artery disease. They proposed that older patients represent a hardy group not vulnerable to the negative effects of hostility. One possible explanation for the difference between Boyle's results and ours is that Boyle et al used a 39-item hostility scale that included questions regarding cynicism, hostile attributions, hostile affect, and aggressive responding, whereas ours only included questions about cynicism. Perhaps age has a stronger interaction with these other components of hostility.

Several potential limitations must be considered when interpreting our results. First, the study population was predominately older men with preexisting stable CHD. Therefore, these findings may not be generalizable to women, younger healthy populations, or populations with recent CV

Table 5. Association Between Baseline Hostility (Entered per Standard Deviation* Increase) and Secondary Events, With Adjustment for Potential Biological and Behavioral Factors

	All-Cause Mortality		Cardiovascular Events†		Any Event	
Model	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Model 1 (adjusted for age)	1.18 (1.07 to 1.30)	0.001	1.17 (1.05 to 1.32)	0.007	1.22 (1.12 to 1.33)	<0.0001
Model 2 (adjusted for potential confounding variables)	1.16 (1.04 to 1.29)	0.009	1.13 (1.00 to 1.29)	0.05	1.18 (1.07 to 1.30)	0.001
Model 3 (add biological factors)	1.13 (1.01 to 1.26)	0.03	1.10 (0.97 to 1.25)	0.15	1.15 (1.04 to 1.27)	0.006
Model 4 (add behavioral factors)	1.08 (0.97 to 1.21)	0.18	1.08 (0.95 to 1.23)	0.23	1.12 (1.01 to 1.23)	0.03
Model 5 (add both biological and behavioral factors)	1.08 (0.96 to 1.20)	0.21	1.07 (0.94 to 1.22)	0.30	1.10 (1.00 to 1.22)	0.06

Model 1=adjusted for age. Model 2=adjusted for age, sex, race, diabetes mellitus, congestive heart failure, antidepressant use, anxiety (HADS-A), depression (C DIS-IV), and LVEF. Model 3=adjusted for all variables in Model 2 plus log C-reactive protein (this was the only biological mediator that resulted in a >5% change in the effect size for hostility). Model 4=adjusted for all variables in Model 2 plus current smoking and physical inactivity. Model 5=adjusted for all variables in Model 2 plus log C-reactive protein, current smoking, and physical inactivity. C DIS-IV indicates Computerized Diagnostic Interview Schedule for the DSM-IV; CI, confidence interval; HADS-A, Hospital Anxiety and Depression Scale; HR, hazard ratio; LVEF, left ventricular ejection fraction.

*The standard deviation of hostility (8-item Cynical Distrust scale) is 2.3 points.

†Cardiovascular events include stroke, transient ischemic attack, myocardial infarction, and heart failure.

events. Second, CV risk factors and potential covariates were measured at the same time as hostility, a single time point, so it was difficult to assess whether certain covariates were mediators or confounders. Regardless of the causal direction, hostility was found to be a strong predictor of secondary events in this cohort and poor health behaviors accounted for a large percentage of this association. Similarly, hostility was also measured at baseline only and therefore it is impossible to know if hostility levels changed over the course of the study period. We believe it is unlikely that hostility levels changed significantly because the Cook-Medley scale has a strong test-retest reliability over multiple years.[6,50] However, we cannot exclude the possibility that hostility acted as a marker of disease severity, which was responsible for the observed increased risk of secondary events.

Third, this study measured cynical hostility and therefore these results may not be observed in other constructs of hostility. Hostility as measured by the Cook-Medley subscale of the Minnesota Multiphasic Personality Inventory (from which the Cynical Distrust scale was derived) is not identical to the free-floating hostility that was originally described in the literature on Type A. However, the Cynical Distrust scale clearly represents a psychosocial factor that increases risk for CV events. Another study found that the global Cook-Medley hostility scale and Cynical Distrust subscale were similarly predictive of CV events.[51] Fourth, our finding that hostility was not significantly associated with the individual outcomes of heart failure, MI, or stroke/TIA may be because of inadequate power. However, Everson et al[27] found a strong association (HR: 2.18, 95% CI: 1.01 to 4.70) between hostility and incident MI in a comparable population size of 1599 men and follow-up time of 10 years with only 60 total events. Fifth, this study used a self-reported measure of hostility, which requires self-awareness and may therefore be susceptible to bias. A recent study by Newman et al[52] concluded that observed hostility is a superior predictor of incident CV events compared with self-reported measures. However, we believe use of a self–reported measure of hostility would only mask a stronger association between hostility and recurrent CV events.

Conclusions

In summary, we found that hostility was associated with the combined outcome of mortality or CV events in a population with stable CHD. The association was primarily attenuated by poor health behaviors. The specific health behaviors identified as moderating this association were smoking and physical inactivity. Future studies should examine the temporal relationship between hostility and CHD risk factors, including poor health behaviors, and should explore the extent by which behavioral and psychosocial interventions may improve CV outcomes in hostile patients.

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Disclosures

None.

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