Association of Optimism and Pessimism With Inflammation and Hemostasis in the Multi-Ethnic Study of Atherosclerosis (MESA)

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Objective: To investigate the association between optimism/pessimism and concentrations of seven inflammation and hemostasis markers. Optimism and pessimism are associated with cardiovascular disease mortality and progression; however, the biological mechanism remains unclear. **Methods:** This cross-sectional study used data from the Multi-Ethnic Study of Atherosclerosis (MESA), a study of 6814 persons aged 45 to 84 years with no history of clinical cardiovascular disease. The Life-Orientation Test-Revised (LOT-R) was used to measure dispositional optimism and pessimism. Regression analyses were used to estimate associations of optimism and pessimism with interleukin (IL)-6, C-reactive protein (CRP), fibrinogen, homocysteine, Factor VIII, D-dimer, and plasmin-antiplasmin, before and after adjustment for sociodemographics, depression, cynicism, health behaviors, body mass index (BMI), hypertension, and diabetes. **Results:** Higher scores on the LOT-R (positive disposition) were related to lower concentrations of IL-6 ($p = .001$), fibrinogen ($p < .001$), and homocysteine ($p = .031$). Associations were stronger for the pessimism subscale. After adjustment for demographics, the percentage differences in inflammatory markers corresponding to a 2-standard deviation increase in pessimism were 6.01% ($p = .001$) for IL-6, 10.31% ($p = .001$) for CRP, 2.47% ($p < .0001$) for fibrinogen, and 1.36% ($p = .07$) for homocysteine. Associations were attenuated but significant after adjustment for sociodemographics, depression, cynical distrust, and behaviors. Further adjustment for hypertension, BMI, and diabetes reduced associations for CRP and IL-6. Pessimism remained associated with a 1.36% ($p = .02$) increase in fibrinogen in the fully adjusted model. Factor VIII, D-dimer, and plasmin-antiplasmin were not associated with the LOT-R or subscales. **Conclusions:** Pessimism is related to higher levels of inflammation. Health behaviors, BMI, hypertension, and diabetes seem to play a mediating role. **Key words:** psychosocial factors, inflammation, coagulation, epidemiology, risk factors.

CVD = cardiovascular disease; **CHD** = coronary heart disease; **MESA** = Multi-Ethnic Study of Atherosclerosis; **HTN** = hypertension; **BMI** = body mass index; **DM** = diabetes mellitus; **LOT-R** = Life-Orientation Test-Revised; **IL-6** = interleukin-6; **CRP** = C-reactive protein; **CES-D** = Center for Epidemiologic Studies Depression scale; **HPA** = hypothalamic-pituitary-adrenal; **MI** = myocardial infarction; **SD** = standard deviation.

INTRODUCTION

Several studies have linked life orientation, as reflected by levels of optimism and pessimism, to cardiovascular disease (CVD) risk (1–8). Optimism is generally defined as the tendency to believe that future expectations and goals will be met, and is different from the absence of depression. Although prior studies have conceptualized optimism and pessimism as opposing poles of a continuum, recent studies showed that they may be better characterized as distinct, negatively related factors (9–12). Optimism has been linked to lower CVD and coronary heart disease (CHD) mortality (5), lower rates of nonfatal myocardial infarction (MI), slower progression of carotid atherosclerosis (4,7,8), better outcomes after coronary artery bypass graft procedures, and fewer restenoses after percutaneous transluminal coronary angioplasty (13). The related construct of pessimism, defined as the general tendency to expect negative outcomes, has been shown to be associated with increased adverse cardiac events, including MI and death from CHD (6), and interacts with socioeconomic status in increasing rates of hypertension (HTN) (14).

There are several mechanisms through which optimism and pessimism may affect CVD and its progression, but these mechanisms have not been well established in empirical studies. Elucidating these mechanisms is important for strengthening causal inferences regarding the health consequences of life orientation and will also enhance our understanding of the etiology of CVD generally. One possible mechanistic pathway involves health behaviors. Life orientation may affect the adoption and maintenance of behaviors, such as diet and physical activity, which are known risk factors for cardiovascular disease. Dispositional optimism has been reported to be associated with nonsmoking, increased physical activity, moderate alcohol consumption, and more fruits, vegetables, and whole grains in the diet (15–17). This finding may result from optimistic persons being more likely to anticipate benefits of behavioral change and, hence, may be more likely to adopt and maintain these changes over time.

It is also plausible that optimism and pessimism affect health through biological mechanisms independent of health behaviors that have been linked to chronic inflammation and CVD. For example, dispositional optimism may down-regulate the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis (18–20). In contrast, a pessimistic disposition may stimulate chronically increased sympathetic tone and stimulation of the HPA axis (20,21), which in turn may induce chronic inflammation and hemostasis. Constructs related to optimism and pessimism, such as positive affect and cynical distrust, have been

shown to be associated with interleukin (IL)-6 and C-reactive protein (CRP) (22,23). However, to our knowledge, the relationships between optimism and pessimism and markers of inflammation and hemostasis have not yet been investigated.

In this study, we explore the relationship between life-orientation and seven circulating inflammation and hemostasis markers that have been previously associated with increased CVD risk: IL-6, CRP, homocysteine, fibrinogen, D-dimer, Factor VIII, and plasmin antiplasmin (24). We use data from the Multi-Ethnic Study of Atherosclerosis (MESA), a large and diverse cohort of individuals ranging in age between 45 and 84 years. We hypothesized that increased optimism and decreased pessimism would be inversely related to levels of inflammation and hemostatic markers, and these associations would be attenuated but remain significant after adjustment for traditional CVD risk factors, behaviors, depression, and cynical distrust. We investigated life orientation as a single bipolar scale, as well as differentiated life orientation into two distinct but negatively related constructs (optimism and pessimism). We hypothesized that stronger associations would be observed with the two-factor approach.

METHODS

MESA is a longitudinal study, supported by the National Heart, Lung, and Blood Institute, with the goal of identifying risk factors for subclinical atherosclerosis and its progression. The study cohort consists of 6814 men and women between the ages of 45 to 84 years, free of clinical CVD at the baseline examination. Individuals were recruited from six field centers around the United States, using a variety of population-based approaches, including lists of area residents, Health Care Financing Administration lists of area residents (for participants ≥65 years of age), area residents enrolled in a union health plan, and random digit dialing. Only persons free of clinical CVD at baseline were eligible. Among those screened and deemed eligible, the participation rate was 59.8%. The cohort was 38% white, 28% black, 22% Hispanic, and 12% Chinese at baseline. Repeat examinations have occurred every 1.5 years to 2 years, with a total of four examinations to date. Details of the study design have been published elsewhere (25). The baseline visit took place between July 2000 and August 2002. The first follow-up visit (during which optimism and pessimism were assessed) occurred between September 2002 and February 2004.

Dispositional optimism, defined as the tendency to expect good outcomes in the future, was measured, using the Life Orientation Test-Revised (LOT-R) at the first follow-up visit. This scale is a six-item revision of the original LOT (9,26). The LOT-R has been shown to have adequate internal consistency (Cronbach's $\alpha = 0.76$), as well as 4-week (0.79) and 13-week (0.79) test-retest reliability (26,27). It includes three positively worded and three negatively worded items. The items were assessed on a 4-point Likert scale, and negatively worded items are reverse-coded and added to the positively worded items, creating a bipolar scale, with higher scores indicating an optimistic disposition. Factor analysis has shown that positively and negatively worded items may be summed separately, and loaded onto two separate subscales, rather than opposing poles (9–12). We investigated both approaches to make appropriate comparisons to prior studies and fully explore the effects of optimism and pessimism on hemostatic and inflammatory factors. We created three partly overlapping measures: six-item full-scale LOT-R, three positively worded items (optimism subscale), and three negatively worded items (pessimism subscale). Higher values on the LOT-R and optimism subscale measures correspond to a more positive orientation, whereas higher levels on the pessimism subscale indicate a negative orientation. Each measure was categorized into quartiles for descriptive analyses, with higher quartiles corresponding to higher scores within the designated scale or subscale.

Inflammatory markers examined include IL-6, CRP, fibrinogen, and homocysteine. Hemostatic markers investigated include Factor VIIIc, D-dimer, and plasmin-antiplasmin. These markers were selected because they are commonly used inflammatory and hemostatis markers that have been previously linked to the occurrence of CVD events or to the development of atherosclerosis (28–35). The inflammatory markers, IL-6, CRP, and fibrinogen, have been reported to be independent risk factors for CVD mortality by contributing to endothelial dysfunction and plaque formation (28,29,31). Homocysteine is thought to induce oxidative stress and inflammation, promoting the formation of foam cells and atherosclerotic plaques, and is therefore considered a marker or precursor for inflammation in this study (36). Markers of hemostasis chosen for this study, D-dimer, Factor VIII, and plasmin-antiplasmin, are part of the coagulation cascade and fibrin cross-linking system (31–35). Up-regulation of the coagulation pathway and dysfunction of the fibrinolytic system are hypothesized to contribute to the prevalence of cerebrovascular accidents and myocardial infarction by increasing susceptibility for ischemic episodes (37). Psychosocial factors like optimism and pessimism may affect components of the inflammation or hemostasis pathway, thereby affecting risk for incident CVD events.

Blood samples were drawn from all participants in the fasting state (or after a noncaffeine, nonfat snack) at the baseline examination, and standardized methods were used for processing and shipping to a central laboratory (Laboratory for Clinical Biochemistry Research, University of Vermont, Burlington, Vermont). IL-6 was measured by an ultrasensitive enzyme-linked immunosorbent assay from R&D systems (Minneapolis, Minnesota), and the laboratory analytical CV for this assay was 6.3%. High-sensitivity CRP and fibrinogen were measured by nephelometry using the BNII nephelometer (N High Sensitivity to CRP and N antiserum to human fibrinogen, Dade Behring Inc., Deerfield, Illinois). The intra-assay and interassay analytical CVs for CRP ranged from 2.3% to 4.4% and from 2.1% to 5.7%, respectively. Corresponding CVs for fibrinogen were 2.7% and 2.6%, respectively. Plasma homocysteine was measured by fluorescence polarization immunoassay with an IMx analyzer (IMx Homocysteine Assay, Axis Biochemicals ASA, Oslo, Norway). The laboratory analytical CV range was 3.8% to 5.1%. Factor VIII coagulant activity was measured, using the Sta-R analyzer (STA-Deficient VIII, Diagnostica Stago, Parsippany, New Jersey) with an analytical CV of 10%, D-dimer by immunoturbidometric methods on the Sta-R analyzer (Liatest D-DI, Liatest VWF, Diagnostica Stago, Parsippany, New Jersey) with an analytical CV of 8%, and plasmin-antiplasmin by a two-site enzyme-linked immunosorbent assay that utilizes two monoclonal antibodies, with an analytical CV of 1.7%.

Sociodemographic information, medical history, health behavior, and cardiovascular risk factor characteristics were obtained by questionnaires during the baseline examination. Education was classified into three groups: less than high school; complete high school or equivalent; and complete college or higher education. Household income over the last 12 months was divided into five categories: <$12,000; $12,000 to $25,000; $25,000 to $40,000; $40,000 to $75,000; and $75,000+. Race and ethnicity were reported based on the participants' responses to questions modeled after the 2000 U.S. Census measure.

Behavioral risk factors included smoking, diet, and physical activity. Cigarette smoking was quantified by pack-years of use. Physical activity was assessed, using a questionnaire adapted from the Cross-Cultural Activity Participation (38), and a composite measure of activity time and level of intensity were used to calculate total intentional exercise activity in metabolic equivalent-minutes/week. Dietary patterns were gauged, using a 120-item, modified-Block style, food frequency questionnaire, and were summarized using four factors derived using factor analysis: "fats and processed meats" (Western); "vegetables and fish" (Chinese); "beans, tomatoes, and refined grains" (Hispanic); and "whole grains and fruits" (prudent) (39).

Other covariates included diabetes, HTN, body mass index (BMI), recent infection, current use of medications known to alter inflammatory response, fasting state, cynical distrust, and depression. Diabetes was defined by the 2003 American Diabetes Association's criteria of fasting plasma glucose >126 mg/dL (40), or use of insulin or other diabetes medications. Hypertension was classified by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure IV 1997 criteria, of

diastolic blood pressure ≥90 mm Hg or systolic blood pressure ≥140 mm Hg or self-reported history of HTN or current use of any hypertensive medications. BMI was calculated as weight over height (in meters) squared. Participants were categorized as having a recent infection if they reported having a cold/flu, sinus, urinary or tooth infection, bronchitis, or pneumonia in the last 2 weeks. Medication use was a binary variable created for individuals who were currently using lipid-lowering medications, nonsteroidal anti-inflammatory drugs, or aspirin. Participants were considered to be fasting if the last thing the person ate or drank was >8 hours before the blood sample was obtained. Depression was measured using the 20-item Center for Epidemiologic Studies-Depression questionnaire (CES-D) (41). Cynical distrust was measured by an eight-item subset of the Cook-Medley hostility scale, which has previously been shown to relate to CVD (42–44).

Biomarkers of inflammation and hemostasis were log-transformed for analyses, and back-transformed to the original metric as geometric means for presentation. In descriptive analyses, we examined gradients of inflammatory and hemostatic markers as well as key covariates across quartiles of optimism, after adjusting for age, sex, and race/ethnicity using χ^2 tests. Linear regression was used to estimate the association of each log-transformed inflammatory and hemostatic marker with the optimism measures after adjustment for potential confounders or mediators. Given that no clear threshold effects were observed in descriptive analyses, optimism and pessimism were investigated as continuous predictors. To facilitate interpretation, exponentiated regression coefficients from regression models with logged continuous outcomes are reported as percent differences in the circulating level of the biomarkers associated with a difference in the optimism or pessimism levels equivalent to 2 standard deviation (SD) in the sample.

The associations of optimism/pessimism with inflammation and hemostasis markers were initially investigated in a base model (model 1), which was adjusted for demographic characteristics (age and sex), fasting state, recent infections, and medication use. In models for subscales, we also adjusted for the opposing LOT-R subscale (i.e., if optimism was the predictor, then the analysis was adjusted for pessimism). Next, the confounding effect of socio-economic position and negative psychosocial factors was assessed in model 2 by adding measures of race/ethnicity, household income and education, depression and cynical distrust to the base model. Model 3 additionally adjusted model 2 for health behaviors, including pack-years of cigarette use, diet, and physical activity. Model 4 further adjusted model 3 for biomedical risk factors, including HTN, BMI, and diabetes mellitus (DM). Heterogeneity in associations of optimism with the outcomes by race/ethnicity, sex, and depression were examined by including appropriate interaction terms in model 1. Of 63 tests, only six tests were statistically significant. Inspection of statistically significant interactions using plots revealed no consistent or substantial effect modification so analyses were subsequently adjusted for these factors.

All reported probability values correspond to two-tailed tests, which were considered significant at the .05 level. The study was approved by Institutional Review Boards at all participating institutions. All subjects gave their written informed consent.

RESULTS

Means for selected characteristics of the full sample (6195), and for those in each quartile of the LOT-R and its subscales are shown in Table 1. The mean age was 62.1 years; the sample was 52% female and 38.5% self-identified as white, 11.8% as Chinese, 27.8% as African American, and 22.0% as Hispanic. The geometric means (SD) of the biomarkers for the full sample were 1.24 pg/mL (1.22 pg/mL) for IL-6, 1.92 mg/dL (3.2 mg/dL) for CRP, 339.31 mg/dL (73.9 mg/dL) for fibrinogen, 8.87 μmol/L (3.75) for homocysteine, 0.22 μmol/L (0.87 μmol/L) for D-dimer, 150.83% (67.0%) for Factor VIII, and 4.43 nM (2.19 nM) for plasmin-antiplasmin.

TABLE 1. Demographic, Behavioral, and Biological Characteristics of Study Population by Categories of Optimism Measures, Adjusted for Age, Race, Sex, MESA 2000 to 2002

Optimism Measure	Mean Score	Mean Age, yrs	% Female	% White	Mean Income, $	Mean Education, yrs	Physical Activity, MET-min/wk	% Current Smokers	Prudent Diet Quartile	Mean BMI	% DM	% HTN	% Recent Infection	% Using Medication
Full sample (n = 6195)		62.2	53	38	48851	13.04	1553	13	2.03	28.34	13	45	22	53
LOT-R	19.9													
Quartile 1	15.7	62	53	40	44842	12.7	1515	15	1.93	28.44	14	45	22	52
Quartile 2	20.1	61.5	51	41	50900	13.42	1609	13	2.01	28.32	12	42	23	53
Quartile 3	22.5	61.9	53	44	55785	13.84	1600	11	2.13	28.37	10	45	22	55
Quartile 4	24	62.7	53	31	50811	12.99	1573	10	2.15	27.85	10	44	24	53
p for trend		.044	.78	.002	.002	.002	.61	.001	.002	.02	.001	.58	.348	.329
Optimism subscale	10													
Quartile 1	6.8	61.8	54	48	47161	12.94	1400	15	1.95	28.37	13	43	22	53
Quartile 2	9.5	61.5	51	46	53895	13.66	1635	13	2.07	28.24	11	42	23	55
Quartile 3	11	61.7	53	38	53013	13.54	1648	12	2.03	28.61	13	45	22	54
Quartile 4	12	62.7	51	29	46618	12.78	1590	11	2.06	28.11	11	46	23	52
p for trend		.001	.21	.001	.008	.33	.02	.004	.10	.09	.29	.03	.77	.222
Pessimism subscale	5.1													
Quartile 1	3	62.6	54	42	55365	13.49	1619	11	2.14	27.99	10	42	23	55
Quartile 2	4	61.2	52	43	54227	13.91	1540	11	2.1	28.49	10	45	23	56
Quartile 3	5.5	61.7	51	40	46701	12.97	1613	14	1.98	28.34	13	44	22	52
Quartile 4	8.3	61.9	53	34	42901	12.56	1478	15	1.89	28.54	15	47	23	51
p for trend		.022	.35	.001	.002	.002	.26	.001	.002	.008	.002	.01	.882	.012

MESA = Multi-Ethnic Study of Atherosclerosis; MET = metabolic equivalent; BMI = body mass index; DM = diabetes mellitus; HTN = hypertension; LOT-R = Life-Orientation Test-Revised.

Of the 6195 participants at the first MESA follow-up examination on whom optimism was measured, 5220 to 5358 participants (depending on the outcome measure) had complete information on all relevant covariates and were included in subsequent analyses. The internal consistency of the LOT-R was 0.73, and was fairly similar (0.66–0.78) across both sexes and all four race/ethnic groups. Factor analysis of the six-item LOT-R confirmed loading of items onto two separate factors, termed "optimism subscale" and "pessimism subscale." Similar reliabilities were observed for the optimism and pessimism subscales (Cronbach's $\alpha = 0.72$ and 0.71, respectively). The correlation between the optimism and pessimism subscales was -0.33 ($p < .0001$). The correlations between the LOT-R and the CES-D and the pessimism subscale and CES-D were -0.35 and 0.30, respectively. The correlations between the LOT-R and cynical distrust and between pessimism and cynical distrust were -0.19 and 0.27, respectively.

Generally, older individuals tended to have higher levels of optimism and lower levels of pessimism although differences in age across quartiles were not graded (Table 1). There was no association between optimism or pessimism and gender. The percent of minority participants increased with increasing levels of both the optimism and the pessimism subscales. The most consistent associations between life orientation measures and socioeconomic indicators were observed for the pessimism subscale: higher pessimism levels were associated with lower income and education in a graded fashion. In general, higher levels of optimism and lower levels of pessimism were also associated with greater physical activity (statistically significant for optimism subscale only), nonsmoking, diets richer in whole grains and vegetables, lower BMI, and less DM. In

all cases, associations were most consistent for the pessimism subscale.

In bivariate analyses (Table 2), higher scores on the LOT-R were generally associated with lower levels of IL-6, CRP, fibrinogen, and homocysteine (although associations with CRP were not statistically significant). No clear patterns were observed for D-dimer, Factor VIII, and plasmin-antiplasmin. In general, the association between the full scale LOT-R and IL-6, CRP, fibrinogen, and homocysteine were driven by the pessimism factor: All four markers were positively associated with higher scores on the pessimism subscale but were not consistently associated with the optimism subscale. D-dimer, Factor VIII, and plasmin-antiplasmin were not consistently associated with the optimism or pessimism subscales and, therefore, are not reported in subsequent analyses.

Table 3 shows the multivariate adjusted percent differences in inflammatory factors associated with a subscale difference equivalent to 2 SD in the optimism and pessimism subscales. These were estimated, using a model with optimism and pessimism subscales entered as continuous variables. After adjustment for age, sex, current infection, current medication use, fasting state, and opposing subscale, a 2-SD increase in the optimism subscale was associated with a 7.67% increase in CRP ($p = .02$). The optimism subscale was not significantly associated with IL-6, fibrinogen or homocysteine in any of the four models. Further adjusting for race/ethnicity, income, education, depression, and cynical distrust (model 2) resulted in attenuation of the association with CRP (4.93% increase, $p = .12$). In the final model, after accounting for effects of health behaviors, HTN, DM, and BMI, a 2-SD increase in the optimism subscale was associated with a

TABLE 2. Geometric Means for Markers of Chronic Inflammation and Hemostatis by Categories of Optimism Measures, Adjusted for Age, Race, Sex, MESA 2000 to 2002

Optimism Measure	IL-6 (pg/mL)	CRP (mg/dL)	Fibrinogen (mg/dL)	Homocysteine (μmol/L)	D-dimer (μg/mL)	Factor VIII (%)	PAP (nM)
Full sample ($n = 6195$)	1.24	1.92	339.31	8.87	0.22	150.83	4.43
LOT-R							
Quartile 1	1.21	1.75	342.1	8.91	0.21	149.75	4.36
Quartile 2	1.22	1.77	336.57	8.83	0.21	150.14	4.29
Quartile 3	1.14	1.67	334.22	8.71	0.21	148.34	4.28
Quartile 4	1.13	1.68	333.45	8.67	0.21	148.56	4.26
p value for trend	.001	.39	<.001	.03	.89	.81	.32
Optimism subscale							
Quartile 1	1.19	1.68	339.61	8.94	0.21	148.03	4.32
Quartile 2	1.2	1.74	337.48	8.77	0.21	150.07	4.35
Quartile 3	1.17	1.76	336.6	8.71	0.22	149.46	4.23
Quartile 4	1.16	1.74	336	8.79	0.21	149.49	4.29
p value for trend	.36	.72	.5	.09	.86	.83	.26
Pessimism subscale							
Quartile 1	1.13	1.64	332.99	8.7	0.21	148.59	4.27
Quartile 2	1.19	1.73	336.8	8.68	0.2	150.88	4.33
Quartile 3	1.2	1.75	338.05	8.94	0.22	149.26	4.3
Quartile 4	1.22	1.81	342.41	8.87	0.21	149.86	4.33
p value for trend	.004	.05	<.001	.005	.09	.79	.64

MESA = Multi-Ethnic Study of Atherosclerosis; IL = interleukin; CRP = C-reactive protein; PAP = plasmin-antiplasmin; LOT-R = Life-Orientation Test-Revised.

TABLE 3. Percent Differences (% diff) in Inflammatory Biomarkers Associated With a 2-Standard Deviation Increase in Optimism and Pessimism Subscales of the LOT-R in MESA 2001 to 2002

LOT-R Subscale	IL-6			CRP			Fibrinogen			Homocysteine		
	% diff	95% CI	p	% diff	95% CI	p	% diff	95% CI	p	% diff	95% CI	p
Optimism												
Model 1	1.95	(−1.52, 5.54)	.27	7.67	(1.43, 14.3)	.02	0.44	(−0.61, 1.51)	.41	−0.71	(−2.14, 0.74)	.33
Model 2	0.66	(−2.9, 4.31)	.72	4.93	(−1.29, 11.5)	.12	−0.46	(−1.55, 0.64)	.41	−1.00	(−2.5, 0.52)	.20
Model 3	2.42	(−1.4, 6.3)	.21	7.80	(1.11, 14.9)	.02	−0.45	(−1.6, 071)	.45	−1.07	(−2.64, 0.51)	.18
Model 4	1.23	(−2.3, 4.9)	.50	5.47	(−0.74, 12.1)	.09	−0.69	(−1.8, 0.44)	.23	−1.22	(−2.78, 0.36)	.13
Pessimism												
Model 1	6.01	(2.4, 9.75)	.001	10.31	(3.91, 17.09)	.001	2.47	(1.4, 3.56)	<.001	1.36	(−0.1, 2.85)	.07
Model 2	3.29	(−0.42, 7.13)	.08	8.16	(1.58, 15.15)	.01	1.77	(0.62, 2.92)	.002	0.69	(−0.88, 2.28)	.39
Model 3	3.71	(−0.2, 7.74)	.06	8.25	(1.42, 15.53)	.02	1.86	(0.66, 3.07)	.002	0.89	(−0.74, 2.54)	.28
Model 4	1.26	(−2.33, 4.98)	.50	4.26	(−1.99, 10.9)	.19	1.36	(0.2, 2.53)	.02	0.62	(−1.0, 2.27)	.45

LOT-R = Life-Orientation Test-Revised; MESA = Multi-Ethnic Study of Atherosclerosis; IL = interleukin; CRP = C-reactive protein; CI = confidence interval.
Model 1: Adjusted for age, sex, current infection, current medication use, fasting state, and opposing subscale; Model 2: additionally adjusts model 1 for race, education, income, depression, and cynical distrust; Model 3: additionally adjusts model 2 for smoking, exercise, and diet; Model 4: additionally adjusts model 3 for BMI, diabetes, and hypertension.

5.47% increase in CRP, but this difference was not quite statistically significant ($p = .09$).

Associations of inflammatory markers with the pessimism subscale were stronger and more consistent than those observed for the optimism subscale. In the base model, a 2-SD increase in the pessimism subscale was significantly related to a 6.01% increase in IL-6 ($p = .001$), 10.31% increase in CRP ($p = .001$), and a 2.47% increase in fibrinogen ($p < .0001$). The 1.36% increase associated with homocysteine was not quite statistically significant ($p = .07$). After sociodemographic and other psychosocial factors were added into the model (model 2), a 2-SD increase in pessimism was still associated with a 3.29% increase in IL-6 ($p = .08$), an 8.16% increase in CRP ($p = .01$) and a 1.77% increase in fibrinogen ($p = .002$). Further adjustment for health behaviors in model 3 did not have much additional effect. A 2-SD increase in pessimism remained associated with higher levels of inflammatory markers: 3.71% for IL-6 ($p = .06$), 8.25% for CRP ($p = .02$), and 1.86% for fibrinogen ($p = .002$). Adjustment for HTN, BMI, and diabetes in model 4 diminished associations with IL-6 and CRP to 1.26% ($p = .5$) and 4.26% ($p = .19$), respectively. Associations of pessimism with fibrinogen remained statistically significant in the fully adjusted model (a 2-SD increase in pessimism was associated with a 1.36% increase in fibrinogen, $p = .02$).

DISCUSSION

Overall, this study showed that higher scores on the LOT-R scale (indicative of higher levels of optimism generally) were associated with lower levels of IL-6, CRP, fibrinogen, and homocysteine, but not D-dimer, Factor VIII, or plasmin-anti-plasmin. When the LOT-R was divided into optimism and pessimism subscales, the pessimism subscale was more strongly associated with inflammatory markers than the optimism subscale, with higher levels of pessimism being associated with higher levels of IL-6, CRP, and fibrinogen in a dose-response fashion. The relationship held after the effects of sociodemographics, negative psychosocial factors, and health behaviors were accounted for. Results are compatible with a mediating role of BMI, HTN, and DM, as adjustment for these factors greatly diminished the association between pessimism and IL-6, CRP, and fibrinogen. Only fibrinogen remained associated with pessimism after full adjustment, which suggests that other unstudied mechanisms may also be involved. In our model, the strength of the associations of pessimism with inflammatory markers are similar to those observed for increase of 10 years of age, but smaller than those observed for diabetes. The magnitudes of the effect sizes are also similar to those reported for cynical distrust in the same sample (22).

Our results add to the growing body of literature on the effect psychosocial factors on CVD development and progression. This study is the first to investigate the associations of optimism and pessimism with inflammation and coagulation. We found that the pessimism subscale had a stronger association with the outcome variables than the full LOT-R or the optimism subscale, and the associations were independent of the effects of depression and cynical distrust. Other studies that have analyzed optimism and pessimism factors separately have found similar results. Räikkönen and Matthews reported that the pessimism subscale had a stronger association with ambulatory blood pressure than either the full-scale LOT-R or the optimism subscale (12). Shen et al. also found that pessimism was a stronger predictor than optimism of worse physical functioning after 6 weeks of cardiac rehabilitation (45). Taken together, these results suggest that pessimism has more pronounced physiologic effects than optimism. However, it is also plausible that the so-called pessimism items (i.e., negatively worded items) are simply better measures of dispositional optimism than the positively worded items, and that dispositional is the relevant psychosocial construct.

In a model adjusted for demographics and pessimism, optimism was associated with higher rather than lower CRP. How-

ever, this finding was not consistent across models or different inflammatory markers and may be spurious. Although optimism specifically has not previously been linked to chronic inflammation, trait positive affect, a similar attribute, was associated with lower IL-6 and CRP among women aged 50 to 74 years in the Whitehall Study (23). Similarly, Ryff et al. reported an inverse association between higher levels of "purpose in life," a factor in the eudaimonic well-being scale, and IL-6 in older women (ages 65 and older) (46). Our findings are congruent with Pressman's and Cohen's "main effect model" which postulates that behavioral and biological pathways mediate the link between psychologic traits and the immune and cardiovascular systems (19). In our study, once behavioral risk factors were controlled for in model 3, the associations with pessimism diminished, as would be expected for a mediating role in this model. Giltay et al. also reported that optimism was associated with health behaviors, such as nonsmoking, increased physical activity, and better diet, adding further support to the model (15). This may occur because people with higher levels of optimism believe they have the ability to change the course of their health and, thereby, tend to adopt better health behaviors. These individuals may also have better self-care behaviors, obtaining more information about their disease and adhering to treatment regimens (19).

Dispositional optimism and pessimism may also directly influence the autonomic nervous system and HPA axis (18–20). Lower levels of blood pressure and cortisol have been reported among those with greater optimism (12,45,47). Similarly, Fredrickson and Levenson demonstrated faster cardiovascular recovery from acute increases in blood pressure and heart rate in response to negative emotional stimuli among those with higher levels of optimism (48). In contrast, a pessimistic disposition may provoke feelings of self-blame, fatalism, and catastrophic thinking, which leads to chronically increased sympathetic tone and cortisol levels (20,21). We did not directly investigate these mechanisms but the persistence of associations with fibrinogen in the fully adjusted models suggests that other mechanisms, perhaps involving physiologic stress processes, could play a role.

The effects of dispositional optimism or pessimism may have long-term systemic effects throughout the life course. Two prospective cohort studies reported that more optimistic individuals have lower rates of MI and mortality from CHD death (5,6) than pessimistic individuals over 10 years to 15 years. Matthews et al. reported that higher pessimism scores resulted in greater increases over time in mean carotid intima-media thickness over the course of 10.4 years (7). The present study adds a plausible mechanism for these findings: If pessimistic orientation is developed in young adulthood, the chronically increased levels of inflammatory factors may contribute to the progression and clinical manifestation of CVD.

We did not find any association between the LOT-R and three measured hemostatic markers (D-dimer, Factor VIII, and plasmin-antiplasmin). We are not aware of other studies that have investigated the association of life-orientation with hemostasis. Although Factor VIII and D-dimer have been shown to increase with acute stress and sympathetic nervous system activation

(49–53), it may be that they do not remain chronically elevated in relationship to trait dispositional pessimism or low optimism.

This study was conducted in a large, diverse, well-characterized sample free of CVD. Although excluding individuals with clinical CVD may have resulted in underestimates of associations, it precluded confounding by disease status. We used the LOT-R, a widely used, validated measure of dispositional optimism, to measure optimism and pessimism (10,11,26,54). We measured life orientation at the first follow-up visit, which was 2 years after the initial visit, when inflammatory markers were measured. However, life orientation is considered a stable trait, and remains relatively unchanged over the course of an individual's lifetime (5). Therefore, it is unlikely that individual scores on the LOT-R changed significantly over the course of the 2 years between visits. Analyses were cross-sectional, limiting causal inferences. However, given that dispositional optimism is a stable trait, usually developed in young adulthood (21,55), it is likely an antecedent factor to mediating health behaviors and biologic pathways that affect CVD progression and outcomes.

In summary, we found that pessimism was associated with higher levels of markers for systemic inflammation in a large, healthy, diverse population. These associations were independent of depression and cynical distrust. Our results are consistent with a mediating role of health behaviors, BMI, HTN, and DM. This may have implications for programs aimed toward primary or secondary prevention of CVD, as the cultivation of optimism may be an important feature of program design.

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