

Joint Effect of Hostility and Severity of Depressive Symptoms on Plasma Interleukin-6 Concentration

EDWARD C. SUAREZ, PhD

Objective: Although interleukin (IL)-6 plays a significant role in cardiovascular disease, little is known about its relation to psychological risk factors, such as hostility and severity of depressive symptoms. The current study examined the joint effects of severity of depressive symptoms and hostility on plasma IL-6 in a sample of 90 healthy, nonsmoking men. **Methods:** After an overnight fast, blood samples for plasma IL-6 and fasting lipids were collected on the same day that the Beck Depression Inventory (BDI) and the Cook-Medley hostility (Ho) scale were administered. Plasma IL-6 was determined using enzymatic-linked immunosorbent assay (ELISA). **Results:** Analyses of logarithmically normalized plasma IL-6 adjusting for age, body mass index (BMI), fasting total cholesterol, high density lipoprotein (HDL), and resting diastolic blood pressure (DBP) revealed a significant BDI by Ho interaction ($p = .026$). Post hoc decomposition revealed that Ho was correlated with log-normalized plasma IL-6 ($r = 0.59, p = .025$) but only among men with BDI scores of 10 and above. Alternatively, BDI was correlated with log-normalized plasma IL-6 ($r = 0.61, p = .003$) but only among men with Ho scores of 23 and higher. Comparisons among BDI/Ho groups indicated that men with high scores on both the BDI and the Ho exhibited the highest median levels of plasma IL-6. **Conclusion:** Hostile men who exhibited above normal levels of depressive symptoms had higher plasma levels of IL-6 suggestive of a subpopulation at increased risk for future cardiac events. **Key words:** severity of depressive symptoms, hostility, plasma interleukin-6, Beck Depression Inventory, Cook-Medley hostility scale, healthy men.

APP = acute-phase protein; **ASCVD** = atherosclerotic cardiovascular disease; **BDI** = Beck Depression Inventory; **BMI** = body mass index; **CHD** = coronary heart disease; **CDC** = Centers for Disease Control; **DBP** = diastolic blood pressure; **ELISA** = enzymatic-linked immunosorbent assay; **HDL** = high density lipoprotein; **Ho** = hostility; **IL** = interleukin; **MCP** = monocyte chemotactic protein; **MDD** = major depressive disorder; **MI** = myocardial infarction; **MRI** = magnetic resonance imaging; **OTC** = over-the-counter; **TC** = total cholesterol; **TNF- α** = tumor necrosis factor- α .

INTRODUCTION

An increasing body of evidence suggests that interleukin (IL)-6 plays a central role in the onset and development of atherosclerotic cardiovascular disease (ASCVD) and the prediction of its clinical expression, such as myocardial infarction (MI). IL-6 is known to be a key mediator of the acute-phase response (APP) which includes the synthesis of C-reactive protein (1), a significant predictor of cardiovascular disease (2). Moreover, IL-6 is thought to stimulate processes contributing to atherosclerotic plaque build-up such as: a) platelet aggregation; b) production of adhesion molecules by the endothelium; c) proliferation by vascular smooth muscle cells; and d) production of tissue factor and monocyte chemotactic protein (MCP)-1 by macrophages (3, 4). In addition to biological effects, IL-6 gene transcripts and protein have been detected in human atherosclerotic lesions (5, 6) and elevated levels of IL-6 have been reported among men and women who show abnormalities of carotid and aorta arteries determined by magnetic resonance imaging (MRI) (7). Lastly, in a 6-year prospective study of apparently healthy men, a single measure of plasma IL-6 taken at entry significantly predicted future risk of MI (8). Taken together, it seems that IL-6 not only affects biological processes involved in the onset and devel-

opment of ASCVD but also characterizes vascular abnormalities and predicts risk of future cardiovascular events in initially healthy persons. Despite the growing importance of IL-6 in all aspects of ASCVD, little is known about its relation to well-recognized psychological risk factors of ASCVD, such as severity of depressive symptoms and hostility.

Evidence indicates that the risk of future cardiac events is associated with the magnitude of depressive symptoms along a gradient and that the severity of depressive symptoms predicts cardiac events in the absence of diagnosis of major depressive episodes (9–11). At this time it is not well understood how severity of depressive symptoms contributes to cardiovascular disease (10). Results of a recent meta-analysis, however, have suggested that IL-6 is significantly associated with major depressive disorder (MDD) (12), even though negative findings have also been reported (13). In contrast, there is a paucity of evidence for the relation of severity of depressive symptoms to IL-6. Two recently published studies, however, have suggested that severity of depressive symptoms and depressed mood are positively associated with IL-6 in healthy, older adults (14, 15).

At this time, there are no published studies of the relation of hostility to IL-6, although recent findings have suggested that hostility is associated with various other inflammatory markers, including proinflammatory cytokines. Stoney and Engerbretson (16) showed that hostility, as measured by the Cook-Medley hostility (Ho) scale (17), was significantly and positively associated with homocysteine, an amino acid known to stimulate IL-6 production (18). In this laboratory, aggression, verbal aggression, and hostility, assessed using the Buss-Perry Aggression Questionnaire (19), were significantly associated with increased in vitro expression of tumor necrosis factor (TNF)- α by stimulated monocytes (20). Like homocysteine, TNF- α is also known to stimulate IL-6 production (1).

Although hostility and severity of depressive symptoms may be independently associated with IL-6, the question arises whether IL-6 covaries as a function of both hostility and severity of depressive symptoms. There is consistent evidence to indicate that hostility is correlated with levels of depressive

From the Department of Psychiatry and Behavioral Science, Duke University Medical Center, Durham, North Carolina.

Address reprint requests to: Edward C. Suarez, PhD, Duke University Medical Center, Box 3328, Durham, NC 27710. Email: ecs.jr@duke.edu

Received for publication June 24, 2002; revision received September 26, 2002.

DOI: 10.1097/01.PSY.0000062530.94551.EA

symptoms in nonclinical samples (21). Moreover, it is recognized that these constructs have overlapping psychological dimensions and often cluster within individuals (21). Thus, individuals who are hostile may be at greater risk for depression due to a lack of social support and/or greater stress (21, 22). Similarly, individuals with depressive symptoms may evaluate the social environment in a cynically hostile manner as a consequence of their negative affective state (22). The overlapping characteristics combined with the overwhelming evidence of significant correlations between measures of hostility and severity of depressive symptoms suggest the relevance of examining the joint effect of hostility and depressive symptoms on cardiovascular health outcomes as well as potential cardiovascular risk factors, such as IL-6. The current study, therefore, examined the joint effect of hostility and severity of depressive symptoms on plasma IL-6 in a sample of healthy men. It was postulated that the severity of depressive symptoms and hostility would jointly and significantly predict IL-6.

METHODS

Sample

Participants were 90 nonsmoking, healthy males (aged 18–45 years) recruited from the general community. The sample comprised 56 Whites, 20 Blacks, 7 Asians, 4 Hispanics, and 3 participants classified as other. Subjects were recruited via advertisements placed in local newspapers and fliers distributed throughout the community. Subjects received monetary compensation for their participation. Interested individuals were medically screened for entry criteria. Participants were determined to be healthy with no past history or current diagnosis of medical conditions that could alter plasma IL-6 (eg, asthma, allergies, arthritis, cancer, cardiovascular disease). All subjects also reported a negative history of psychiatric ailments with none reporting ever using antidepressant medications. All subjects were free of acute infections or injuries during the 2 weeks before their laboratory session. Subjects were also free of all prescription medications and over-the-counter (OTC) preparations, including daily low-dose aspirin, for the 2 weeks before study participation. Written informed consent was obtained before study participation. This protocol was approved by the institutional review board.

Procedure

Blood samples were collected on the same day the subject completed the hostility and severity of depressive symptoms scales. Subjects arrived between the hours of 8:00 AM and 9:00 AM. Subjects fasted for 12 hours before their laboratory appointment. On arrival, subjects were seated in a reclining chair and a 21-gauge butterfly needle was inserted into a forearm vein. After 30 minutes, blood samples were collected.

After blood samples were collected, subjects completed the 21-item BDI (23), the 50-item Cook-Medley Ho scale (12), and a short background

questionnaire. The BDI and the Ho have been reported to have good psychometric properties including adequate internal validity, good test-retest reliability, and construct validity (24, 25). Evidence suggests that BDI scores are positively correlated with clinical ratings of depression (24). Similarly, evidence for convergent validity has also been reported for the Ho scale (25). For the BDI, participants were instructed to reflect on the week before study participation when responding to the questions.

Assessment of Interleukin-6, Lipids, and Blood Pressure

For plasma IL-6, blood samples were collected in 7-ml tubes with EDTA. Whole blood samples remained chilled for approximately 30 minutes until delivered to the laboratory. Blood samples were spun and plasma was stored at -40°C until time of assay. Plasma IL-6 levels were measured by an enzyme-linked immunosorbent assay (ELISA) kit commercially available from Pierce-Endogen (Rockford, IL). Samples were assayed in duplicate, and IL-6 concentrations were derived from a standard curve. The detectable limit for plasma IL-6 was $<1\text{ pg/mL}$ and the intra- and interassay coefficients of variation were $<5\%$ and $<10\%$, respectively.

Assessments of fasting TC and HDL cholesterol were conducted at a CDC-certified laboratory using standard enzymatic methods. Resting blood pressure was obtained by using a Dinamap blood pressure monitor (1876 \times , Critikon Corp., Tampa, FL) while the subject was seated. Measurements were taken at 1-minute intervals throughout a 5-minute period, and a mean blood pressure was calculated.

RESULTS

Subject characteristics are presented in Table 1. Consistent with previous studies, the BDI and Ho scores were significantly correlated (Pearson $r = 0.47$, $p < 0.001$). In this sample, BDI scores ranged from 0 to 28, with 22% of the sample scoring 10 and above, a cutoff score suggested by Beck and Steer (26) and Kendall et al. (27) to indicate at least mild levels of depressive symptoms. Using the Beck and Steer (26) criteria, all of the men in this study with BDI scores of 10 and above were classified as having either mild (BDI scores 10–18) or moderate (BDI scores 19–30) levels of depressive symptoms. Previous studies have indicated that even mild to moderate levels of depressive symptoms are associated with greater risk for mortality among cardiac patients (28) and with biological risk factors of coronary heart disease in apparently healthy persons (29).

Ho scores ranged from 3 to 37. For the Ho scale, an a priori cutoff score of 23 and above was used to establish Ho groups. Previous studies in this laboratory have shown that men with Ho scores of 23 and above exhibit increased cardiovascular and hormonal reactivity to anger arousal (30, 31), lower β -adrenergic receptor number (32), and reduced β -adrenergic

TABLE 1. Characteristics of Study Participants ($N = 90$)

	Mean	SD	Range
Age (yr)	26.1	6.8	18–46
Body mass index (kg/m^2)	24.4	3.3	19–38.5
Total cholesterol (mg/dL)	160.2	38.7	91–289
HDL cholesterol (mg/dL)	42.9	10.2	19–73
Resting diastolic blood pressure (mm Hg)	75.5	9.0	50–101
Beck Depression	4.9	5.2	0–28
Cook-Medley hostility	19.1	7.7	3–37
Plasma IL-6 (pg/mL)	3.14	5.00	.01–20.6

DEPRESSIVE SYMPTOMS, HOSTILITY, AND IL-6

responsiveness to β -agonist (33). Using this criterion, 31.1% of the sample scored high on the Ho scale.

Plasma concentrations of IL-6 were skewed so values were normalized using the logarithmic transformation formula ($\log_{10}(X + 1)$) as suggested by Kirk (34). Preliminary univariate analyses revealed that a log-normalized concentration of IL-6 was not significantly associated with age ($r = -0.06$); BMI ($r = -0.02$); fasting TC ($r = -0.08$); HDL cholesterol ($r = -0.02$); and resting DBP ($r = -0.08$). Although these variables were not associated with plasma IL-6 in this study, previous studies have indicated that these variables are positively related to plasma IL-6 (37, 38, 42). Therefore, these factors were retained in the regression models to eliminate the possibility of confounding as well as to make the analyses more comparable with the analytic strategy employed by Ridker et al. (8) in determining the relation of log-normalized plasma IL-6 to future risk of MI.

To test the hypothesis of a joint effect of hostility and depressive symptoms on plasma IL-6, a series of regression equations were performed. The first regression model examined the percent of variance (R^2) of log-transformed IL-6 accounted by all of the covariates. In Step 2, the main effects of Ho and BDI, entered as continuous variables, were added to the model and changes in variance accounted (ΔR^2) were examined. The third step examined the interaction of Ho and BDI by inspecting the ΔR^2 change from the R^2 accounted by the model in Step 2. All analyses were conducted using SAS software (35).

Results indicated a significant BDI by Ho score interaction ($\Delta R^2 = 0.0572$, $F\Delta = 5.13$, $p = .026$). Decomposition of this interaction showed that, among persons with BDI scores of 10 and above, Ho scores were positively and significantly associated with log-transformed IL-6 (partial $r(19) = 0.59$, $p = .025$). In contrast, among subjects with BDI scores of 9 and below, Ho scores were not associated with IL-6 (partial $r(68) = -0.03$, NS). Conversely, among men with Ho scores of 23 and above, BDI scores were positively and significantly associated with log-normalized IL-6 (partial $r(27) = 0.61$, $p = .003$). In contrast, in men with low to moderate Ho scores (ie, $Ho < 23$), BDI scores were not associated with log-normalized IL-6 values (partial $r(61) = -0.07$, NS). Given the significance of the two-way interaction, the main effects for BDI and Ho were not examined, although both effects were not significant.

To further illustrate these findings and to facilitate the comparison of these data with plasma IL-6 levels in men from the Physicians' Health Study (8), we plotted unadjusted medians for BDI/Ho groups. As shown in Figure 1, median plasma concentrations of IL-6 were higher among men who had high scores on both the Ho and BDI.

DISCUSSION

It is widely acknowledged that ASCVD is fundamentally a chronic inflammatory disorder (36). Consistent with this view, IL-6 has been shown to predict future risk of MI and to contribute to processes leading to ASCVD (37). The current

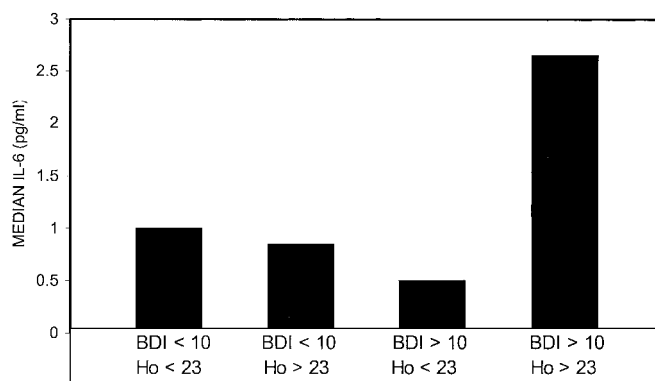


Fig. 1. Unadjusted median for IL-6 by BDI and Ho groups.

study examined the relation of plasma IL-6 as a function of both severity of depressive symptoms and hostility. Results indicated a significant joint effect of hostility and severity of depressive symptoms on plasma IL-6 levels. This interaction predicted plasma IL-6 concentrations even after statistical adjustment for age, BMI, lipids, and resting DBP, factors associated with IL-6 (8, 37, 38, 42). Statistical decomposition of this two-way interaction revealed that, among men with BDI scores of 10 and above, Ho scores were significantly and positively associated with log-normalized plasma IL-6. Alternatively, among men with Ho scores of 23 and above, BDI scores were significantly and positively associated with log-transformed plasma IL-6. Lastly, group comparisons among BDI/Ho groups indicated that men who scored high on both the BDI and Ho scales exhibited the highest median concentration of plasma IL-6 relative to all other groups.

Results from the Physicians' Health Study indicated that increasing levels of plasma IL-6 are associated with an increasing number of traditional risk factors (eg, hypertension, hyperlipidemia, smoking) (8). The current findings are the first to demonstrate that higher plasma IL-6 levels are also associated with the presence of both hostility and severity of depressive symptoms. That plasma IL-6 predicts future risk of cardiovascular events, as well as all-cause mortality, leads to the possibility that men who are both hostile and exhibit depressive symptoms, even in the mild to moderate range, are at heightened risk for all-cause mortality and cardiac events (37). Consistent with this speculation, one study has reported greater all-cause mortality among hostile individuals with depressive symptoms (39). With this one exception, no other study has examined the combined effect of hostility and severity of depressive symptoms on health outcomes or cardiovascular end points. The current observations, therefore, add relevance to the argument for examining the joint effect of hostility and severity of depression in predicting outcome measures in epidemiological studies of cardiovascular disease as well as laboratory studies of biological risk factors.

The current study did not address possible mechanisms that could explain these observations. However, inclusion criteria (eg, healthy, free of any acute medical conditions, nonsmokers, no medications whether prescribed or over-the counter)

and statistical controls (eg, age, BMI, resting DBP, lipids) implemented in this study support the conclusion that higher plasma IL-6 levels among hostile men with mild to moderate symptoms of depression are not mediated by these factors. Thus, elevated IL-6 levels in hostile men with depressive symptoms may be due, in part, to other factors, possibly stress-related in nature (43, 44).

The current study has limitations. First, the participants were nonsmoking, healthy males. From a medical perspective, these men are considered to be at minimal risk for future cardiac events, such as MI. It is acknowledged, however, that approximately one-half of the risk for MI is accounted by conventional risk factors (46) thus allowing for the possibility that nontraditional risk factors, such as hostility and severity of depressive symptoms, are relevant in determining risk. It is interesting to note, therefore, that the median plasma IL-6 level for men with high BDI and Ho scores fell in the highest quartile of plasma IL-6 observed in the Physicians' Health Study, a group found to be at high risk for MI (8). Additional comparisons reveal that median plasma levels of IL-6 for men with low Ho/low BDI, high Ho/low BDI, and low Ho/high BDI scores fell in the lowest quartile of plasma IL-6, a group found to be at low risk in the Physicians' Health Study. Thus, even in men considered medically at low risk for future cardiac events, the plasma levels of IL-6 in men with high Ho and BDI scores are comparable with those of initially healthy men who subsequently experienced an MI during a 6-year follow-up (8).

A second study limitation is the single measure of plasma IL-6. Blood samples were collected while experimentally controlling for factors that could influence circulating IL-6 levels, such as health status, smoking, injury, psychiatric conditions, medications, and low-dose aspirin. Although blood samples were collected at a uniform time of day following an overnight fast, variations in circulating levels of IL-6 cannot be ruled out (40). It is likely, however, that any diurnal variation would contribute to a greater error that would lead to an underestimation of the true association. Although a single measure of IL-6 may not provide a true assessment of an individual's variation in IL-6, one study has reported an intraclass correlation of 0.87 for plasma IL-6 when it was measured repeatedly over a 1-month period (41). The relative stability of plasma IL-6 levels over a 1-month period (in conjunction with the prognostic significance of a single measure of IL-6 in assessing future risk of MI) argues that a single measure of plasma IL-6 may be satisfactory in assessing risk.

Lastly, the study included only men. Previous studies have suggested that plasma IL-6 is also associated with increased risk of cardiovascular disease in women (45). Currently, this laboratory is conducting a study to examine the joint effect of Ho and BDI on plasma IL-6 in women. Given that women score higher on BDI and lower on Ho than men, the relation of IL-6 to measures of depressive symptoms and hostility may differ in women. In addition, the relation of plasma IL-6 to hostility and severity of depressive symptoms may be moder-

ated by ovarian hormones, given that estrogen may reduce IL-6 production (38).

In conclusion, the current study demonstrates a joint effect of hostility and severity of depressive symptoms on the plasma concentration of IL-6 in apparently healthy men. This observation was independent of the effects of traditional risk factors of cardiovascular disease that are known to influence plasma IL-6, such as age, smoking, BMI, blood pressure, and lipids. The current findings raise the possibility that, among hostile men with depressive symptoms, plasma IL-6 is either a marker for future risk of ASCVD or is a pathophysiological mechanism leading to increased risk of ASCVD. Whatever the case may be, the current findings broaden our understanding of how hostility in conjunction with depressive symptoms may impact cardiovascular disease risk via elevations in plasma IL-6. It remains to be seen whether these observations can be replicated in women and whether this relationship can be moderated by prophylactic interventions that include lifestyle changes and/or anti-inflammatory therapies, both known to reduce the risk of cardiovascular disease (46).

This work was supported by National Heart, Lung, and Blood Institute grants HL-56105 and HL-67459. The author thanks Melinie Tirronen, Sarah S. Rush, and Tara N. Pennington for their efforts in data collection and Tony Zimmerman for performing the IL-6 assay. The author also thanks Carlos Mendes de Leon, PhD, for his insight on the potential application of the current findings to epidemiological studies of the joint effect of hostility and severity of depressive symptoms on cardiovascular outcomes.

REFERENCES

1. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990;265:621-36.
2. Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996; 144:537-47.
3. Barton BE. The biological effects of interleukin-6. *Med Res Rev* 1996; 16:87-109.
4. Ikeda U, Ito T, Shimada K. Interleukin-6 and acute coronary syndrome. *Clin Cardiol* 2001;24:701-4.
5. Seino Y, Ikeda U, Ikeda M, Yamamoto K, Misawa Y, Hasegawa T, Kano S, Shimada K. Interleukin-6 gene transcripts are expressed in human atherosclerotic lesions. *Cytokine* 1994;6:87-91.
6. Rus HG, Vlaicu R, Niculescu F. Interleukin-6 and interleukin-8 protein and gene expression in human arterial atherosclerotic wall. *Atherosclerosis* 1996;127:263-71.
7. Weiss CR, Arai AE, Bui MN, Agyeman KO, Waclawiw MA, Balaban RS, Cannon RO III. Arterial wall MRI characteristics are associated with elevated serum markers of inflammation in humans. *J Magn Reson Imaging* 2001;14:698-704.
8. Ridker PM, Rifai N, Stampfer MJ, Hennekens CH. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;101:1767-72.
9. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry* 1998;155:4-11.
10. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation* 1999;99:2192-217.
11. Penninx BW, Beekman AT, Honig A, Deeg DJ, Schoevers RA, van Eijk JT, van Tilburg W. Depression and cardiac mortality: results from a community-based longitudinal study. *Arch Gen Psychiatry* 2001;58: 221-7.
12. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression

DEPRESSIVE SYMPTOMS, HOSTILITY, AND IL-6

- and stressors to immunological assays: a metaanalytic review. *Brain Behav Immun* 2001;15:199–226.
13. Reif W, Pilger F, Ihle D, Bosmans E, Egyed B, Maes M. Immunological differences between patients with major depression and somatization syndrome. *Psychiatry Res* 2001;105:165–74.
 14. Dentino A, Pieper CF, Rao MK, Currie MS, Harris T, Blazer DG, Cohen HJ. Association of interleukin-6 and other biologic variables with depression in older people living in the community. *J Am Geriatr Soc* 1999; 47:6–11.
 15. Lutgendorf SK, Garand L, Buckwalter KC, Reimer TT, Hong SY, Lubaroff DM. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. *J Gerontol A Biol Sci Med Sci* 1999;54: M434–9.
 16. Stoney CM, Engerbretson TO. Plasma homocysteine concentrations are positively associated with hostility and anger. *Life Sci* 2000;66:2267–75.
 17. Cook WW, Medley DM. Proposed hostility and pharisaic-virtue scales for the MMPI. *J Appl Psychol* 1954;38:414–8.
 18. van Aken BE, Jansen J, van Deventer SJ, Reitsma PH. Elevated levels of homocysteine increase IL-6 production in monocytic Mono Mac 6 cells. *Blood Coagul Fibrinolysis* 2000;11:159–64.
 19. Buss AH, Perry M. The aggression questionnaire. *J Pers Soc Psychol* 1992;63:452–9.
 20. Suarez EC, Lewis JG, Kuhn CM. The relation of aggression, hostility, and anger to lipopolysaccharide-stimulated tumor necrosis factors (TNF)- α by blood monocytes from normal men. *Brain Behav Immun*. In press.
 21. Felsten G. Hostility, stress, and symptoms of depression. *Person Individ Diff* 1996;21:461–7.
 22. Raynor DA, Pogue-Geile F, Kamarck TW, McCaffery JM, Manuck SB. Covariation of psychosocial characteristics associated with cardiovascular disease: genetic and environmental influence. *Psychosom Med* 2002; 64:191–203.
 23. Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: 25 years of evaluation. *Clinical Psych Review* 1988;8:77–100.
 24. Nezu AM, Nezu CM, McClure KS, Zwick ML. Assessment of depression. In: Gotlib IH, Hammen CL, editors. *Handbook of depression*. New York: Guilford Press; 2002, p. 61–85.
 25. Smith TW, Frohm KD. What's so unhealthy about hostility? Construct validity and psychological correlates of the Cook and Medley Ho scale. *Health Psychol* 1985;4:503–20.
 26. Beck AT, Steer RA. *Beck Depression Inventory Manual*. Toronto: Harcourt, Brace, Jovanovich; 1987.
 27. Kendall PC, Hollon S, Beck AT, Hammen CL, Ingram RE. Issues and recommendations regarding use of the Beck Depression Inventory. *Cognit Ther Res* 1987;11:289–99.
 28. Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and 1-year changes in depression symptoms after myocardial infarction. *Circulation* 2002;105: 1049–53.
 29. Stein PK, Carney RM, Freedland KE, Skala JA, Jaffe AS, Kleiger RE, Rottman JN. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. *J Psychosom Res* 2000;48:493–500.
 30. Suarez EC, Williams RB. Situational determinants of cardiovascular and emotional reactivity in high and low hostile men. *Psychosom Med* 1989;51:404–18.
 31. Suarez EC, Kuhn CM, Schanberg SM, Williams RB, Zimmermann EA. Neuroendocrine, cardiovascular, and emotional responses of hostile men: the role of interpersonal challenge. *Psychosom Med* 1998;60:78–88.
 32. Suarez EC, Shiller AM, Kuhn CM, Schanberg SM, Williams RB, Zimmermann EA. The relationship between hostility and β -adrenergic receptor physiology in healthy young males. *Psychosom Med* 1997;59:481–7.
 33. Suarez EC, Sherwood A, Hinderliter AL. Hostility and adrenergic receptor responsiveness: evidence of reduced β -receptor responsiveness in hostile men. *J Psychosom Res* 1998;44:261–77.
 34. Kirk RE. *Experimental design: procedure for the behavioral sciences*. Belmont (CA): Brooks/Cole Publishing; 1968. p. 65.
 35. SAS Institute, Inc. *SAS/STAT user's guide, version 6*. Cary (NC): SAS Institute, Inc.; 1990.
 36. Ross R. Mechanisms of disease: atherosclerosis and inflammatory disease. *N Engl J Med* 1999;340:115–26.
 37. Yudkin JS, Kumari M, Humphries SE, Mohamed-Ali V. Inflammation, obesity, stress, and coronary heart disease: is interleukin-6 the link? *Atherosclerosis* 2000;148:209–14.
 38. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: downregulation with essential fatty acids, ethanol, and pentoxifylline. *Med Hypotheses* 1999;52:465–77.
 39. Barefoot JC, Williams RB, Siegler IC, Schroll M. Depressive affect, hostility, and socioeconomic status (SES): interrelationships and joint effects on health. *Psychosom Med* 1995;57:66.
 40. Sothern RB, Roitman-Johnson B, Kanabrocki EL, Yager JG, Fuerstenberg RK, Weatherbee JA, Young MR, Nemchausky BM, Scheving LE. Circadian characteristics of interleukin-6 in blood and urine of clinically healthy men. *In Vivo* 1995;9:331–9.
 41. Rao KMK, Pieper CS, Currie MS, Cohen HJ. Variability of plasma IL-6 and crosslinked fibrin dimers over time in community-dwelling elderly subjects. *Am J Clin Pathol* 1994;102:802–5.
 42. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension* 2001;38:399–403.
 43. Steptoe A, Willemsen G, Owen N, Flower L, Mohamed-Ali V. Acute mental stress elicits delayed increases in circulating inflammatory cytokine levels. *Clin Sci* 2001;101:185–92.
 44. Paik IH, Toh KY, Lee C, Kim JJ, Lee SJ. Psychological stress may induce increased humoral and decreased cellular immunity. *Behav Med* 2000; 26:139–41.
 45. Ridker PM, Hennekens CH, Buring J, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–43.
 46. Manson JE, Tosteson H, Ridker PM, Satterfield S, Hebert P, O'Connor GT, Buring JE, Hennekens CH. The primary prevention of myocardial infarction. *N Engl J Med* 1992;326:1406–16.