Relation of Depressive Symptoms to C-Reactive Protein and Pathogen Burden (Cytomegalovirus, Herpes Simplex Virus, Epstein-Barr Virus) in Patients With Earlier Acute Coronary Syndromes

Gregory E. Miller, PhD, Kenneth E. Freedland, PhD, Stephen Duntley, MD, and Robert M. Carney, PhD

Despite mounting evidence that depressive symptoms increase the risk of morbidity and mortality in patients who have coronary artery disease, little is known about the biologic mechanisms that underlie this association. This study examined whether depressive symptoms are associated with markers of infection and inflammation that have been implicated in the pathogenesis of coronary artery disease. Sixty-five patients who were recovering from an acute coronary syndrome were enrolled (63% men; mean age 61 years, 90% white). Depressive symptoms were assessed through self-report and observer ratings; the inflammatory molecules C-reactive protein, interleukin-6, and tumor necrosis factor-α were measured in serum, as were antibody titers to 3 latent viruses associated with atherosclerosis. Patients who had more severe depressive symptoms exhibited higher levels of C-reactive protein ($r = 0.27$, $p = 0.03$) and higher rates of seropositivity to the latent viruses ($r = 0.41$, $p = 0.001$). These effects were large in magnitude: patients in the highest tertile of the depression distribution had C-reactive protein levels >50% higher than did patients in the middle and lowest tertiles; they also were 2 times as likely to show evidence of infection with all 3 latent viruses. Disparities in the extent, severity, or management of cardiac disease were not responsible for these associations. These findings provide evidence that depressive symptoms are associated with increases in C-reactive protein and pathogen burden in patients who have coronary artery disease. In doing so, they highlight a mechanism through which depressive symptoms might foster morbidity and mortality among patients who have cardiac disease. ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:317–321)

Depression is a common feature of coronary artery disease (CAD). About 20% of patients who have CAD meet diagnostic criteria for major depression,[1,2] and an even larger percentage develops difficulties with mood that are below the diagnostic threshold.[3] Among patients who recover from an acute coronary syndrome (ACS), the presence of depressive symptoms is associated with a two- to fourfold increase in cardiac morbidity and mortality rates, independent of disease severity, treatment regimen, and standard risk factors.[4–8] This is true even when the symptoms are of a subclinical nature, i.e., not sufficiently persistent or disabling to merit a diagnosis of major depression.[4,5] Despite this robust pattern of findings, little is known about the underlying mechanisms. There has been much speculation that depression accelerates CAD progression by fostering long-term infections and activating inflammatory processes.[9–13] We tested this hypothesis by examining whether depressive symptoms, even of a subclinical nature, are associated with infectious and inflammatory processes implicated in the pathogenesis of CAD.

METHODS

Patients: The sample consisted of 65 patients who had been recruited from cardiology practices at the Barnes-Jewish Hospital at Washington University School of Medicine (St. Louis, Missouri). All patients were recovering from an ACS and had myocardial infarction, bypass surgery, or coronary angioplasty ≥3 months previously. Patients who agreed to participate were contacted and, provided they were stable, took part in an eligibility screening during which a nurse collected medical history. Candidates were excluded if they had (1) severe cognitive impairment, excessive substance/alcohol use, or psychiatric conditions other than depression or anxiety; (2) severe co-morbid medical conditions including advanced malignancy, diabetic neuropathy, pulmonary disease, or sleep disorder; or (3) valvular heart disease, active congestive heart failure, or an implantable pacemaker. Patients who met eligibility criteria were scheduled

From the Department of Psychology, University of British Columbia, Vancouver, British Columbia, Canada; and the Departments of Psychiatry and Neurology, Washington University School of Medicine, St. Louis, Missouri. This research was supported by grants from the American Heart Association, Dallas, Texas; the National Alliance for Research on Schizophrenia and Depression, Great Neck, New York; the National Heart, Lung, and Blood Institute, Bethesda, Maryland; the Michael Smith Foundation for Health Research, Vancouver, British Columbia, Canada; and the Canadian Institutes of Health Research, Ottawa, Ontario, Canada. Manuscript received June 23, 2004; revised manuscript received and accepted September 20, 2004.

Address for reprints: Gregory E. Miller, PhD, Department of Psychology, University of British Columbia, 2136 West Mall, Vancouver, British Columbia V6T 1Z4, Canada. E-mail: gemiller@psych.ubc.ca.

0002-9149/05/$–see front matter
doi:10.1016/j.amjcard.2004.09.026

for a 2-night stay at the Washington University Sleep Medicine Center as part of a larger project. The protocol was approved by the institutional review board of Washington University School of Medicine.

Depressive symptoms: Depressive symptoms were assessed by self-report and observer ratings. During their visit to the sleep laboratory, patients completed the Beck Depression Inventory, a widely used 21-item measurement of depressive symptoms.[14] Observer ratings were obtained at the eligibility screening, when a nurse administered the 17-item Hamilton Rating Scale for Depression[15] as part of a diagnostic interview.[16] These measurements showed high levels of internal consistency in this sample ($\alpha = 0.94, 0.89$). Because scores on the Beck Depression Inventory and Hamilton Rating Scale for Depression were strongly related ($r = 0.86$, $p < 0.001$), we z-transformed and averaged the scores to form an index that reflected the severity of depressive symptoms. This procedure diminishes random error and therefore boosts statistical power. Although the results presented in the following were produced with this composite index of symptoms, virtually identical findings emerge when the Beck Depression Inventory and Hamilton Rating Scale for Depression are used as stand-alone measures.

Inflammatory and infectious markers: We assessed the expression of 3 inflammatory molecules, C-reactive protein (CRP), interleukin-6, and tumor necrosis factor-α, implicated in the development and progression of CAD.[17,18] Blood was drawn through antecubital venipuncture ≤1 hour of awakening at the Sleep Medicine Center. After the blood had been centrifuged for 25 minutes at 1,000*g*, the serum was aspirated, divided into aliquots, and frozen at −70°C. At the end of the study, samples were thawed and run in a single batch. CRP was quantitated by high-sensitivity immunoassay on a BN-100 nephelometer (Dade-Behring, Deerfield, Illinois). This assay has a sensitivity of 0.175 mg/L and intra- and interassay coefficients of variation <10%. Interleukin-6 and tumor necrosis factor-α were measured with a commercially available immunoassay (Linco Research, St. Louis, Missouri) on a Luminex 100. These assays have a sensitivity of <3.2 pg/ml and intra- and interassay coefficients of variation of <12%.

To evaluate latent infections that might accelerate CAD, we used thawed serum to quantify antibodies against 3 pathogens. Immunoglobulin-G antibodies to cytomegalovirus and herpes simplex virus were measured with commercially available immunoassays (cytomegalovirus immunoglobulin-G, Vidas; herpes simplex virus immunoglobulin-G, Dade-Behring) on a Vitek Immunodiagnostic System (bioMerianx Corp., Durham, North Carolina). Immunoglobulin-G antibodies to Epstein-Barr virus were quantified with a commercially available immunofluorescence technique (Merifluor, Meridian Diagnostics, Cincinnati, Ohio). Intra-assay coefficients of variation for all assays were <10%. Patients were categorized as having recently active infections when they showed values of ≥6 Bodansky's units for cytomegalovirus, ≥10 Bodansky's units for Epstein-Barr virus, and net absorbance ≥0.20 for herpes simplex virus. Because the total number of latent infections is a stronger determinant of inflammation than any single infection, we created a "pathogen burden" score for each patient that reflected the number of organisms for which that patient was seropositive.

Demographic and medical characteristics: Relations between depressive symptoms and biologic outcomes can arise from residual confounding with demographic characteristics, medical history, disease severity, or treatment received. To examine this possibility, we gathered data on these variables by chart reviews and interviews about medical history. Because inflammatory molecules can be increased due to acute infection, a complete blood count was done on blood drawn during visits to the Sleep Medicine Center. One patient who showed evidence of active infection was excluded from the analyses.

Statistical analyses: Because markers of inflammation and pathogen burden were distributed in a non-normal fashion, rank-order correlations were used to quantify relations between depression and outcomes. To clarify the nature of significant associations, the sample was later divided into 3 evenly sized groups that corresponded to patients who did not have depressive symptoms (Beck Depression Inventory median score 1, Hamilton Rating Scale for Depression median score 1) and those who had symptoms of mildly severe depression (median scores 14 and 10) or moderately severe depression (median scores 25 and 19). To evaluate disparities between these groups, Mann-Whitney U tests (for continuous outcomes) and Kendall's τ_b (for categorical outcomes) were used. Two-tailed tests of significance were employed. All data are presented as mean ± SEM, unless otherwise noted.

RESULTS

Demographic, psychiatric, and cardiovascular characteristics of patients are presented in Table 1.

Depressive symptoms and markers of inflammation and infection: To the extent that they had more severe depressive symptoms, patients showed higher levels of CRP ($r = 0.27$, $p = 0.03$). Further analyses showed that patients in the highest symptom tertile had significantly more CRP than did patients in the middle tertile ($z = 2.0$, $p = 0.04$) and lowest tertile ($z = 2.2$, $p = 0.03$). The latter groups did not differ from each other ($z = 0.8$, $p = 0.78$). The median CRP values for the highest, middle, and lowest tertiles were 3.6, 2.4, and 2.4 mg/L, respectively. Thus, patients who had moderately severe symptoms had CRP levels >50% than did patients who had mild or negligible symptoms (Figure 1). Depressive symptoms were unrelated to levels of interleukin-6 ($r = 0.05$, $p = 0.72$) and tumor necrosis factor-α ($r = 0.17$, $p = 0.21$). There was no association between psychiatric diagnosis (major depression vs minor depression vs no diagnosis) and levels of inflammatory molecules ($p > 0.37$).

There was also a relation between depressive symptoms and pathogen burden. To the extent that they endorsed more severe depressive symptoms, patients were seropositive for a larger number of latent viruses (r

TABLE 1 Patients' Characteristics (n = 65)

Beck Depression Inventory	14.0 ± 1.4
Hamilton Rating Scale	10.9 ± 1.1
CRP (mg/L)	3.7 ± 0.5
Interleukin-6 (pg/ml)	8.0 ± 4.0
Tumor necrosis factor-α (pg/ml)	8.7 ± 0.8
Age (yrs)	61 ± 1
Women	38%
White/black	91%/9%
Married	70%
Daily smoker, current/former	14%/46%
Body mass index (kg/m^2)	29 ± 1
Diabetes mellitus	22%
Hypertension	58%
Angina pectoris	63%
Myocardial infarction	50%
Time since infarction (months)	18 ± 6
Killip's class >I	15%
Congestive heart failure	17%
Atrial or ventricular arrythmia	7%
Peripheral vascular disease	5%
Cerebrovascular accident	9%
Coronary angioplasty	53%
Coronary bypass surgery	36%

Values are mean ± SEM or percentages.

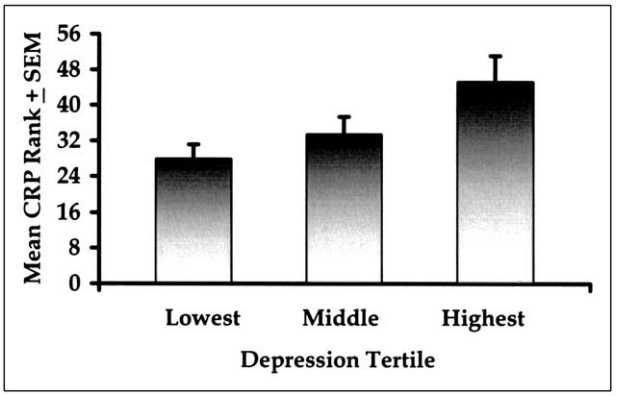

FIGURE 1. Patients in the highest depression tertile exhibited significantly higher CRP levels than did patients in the middle tertile (p = 0.04) and lowest tertile (p = 0.03), who did not differ from each other (p = 0.78). The groups roughly correspond to patients who had moderate, mild, and negligible symptoms of depression. CRP values are presented as ranks within the sample ± SEM.

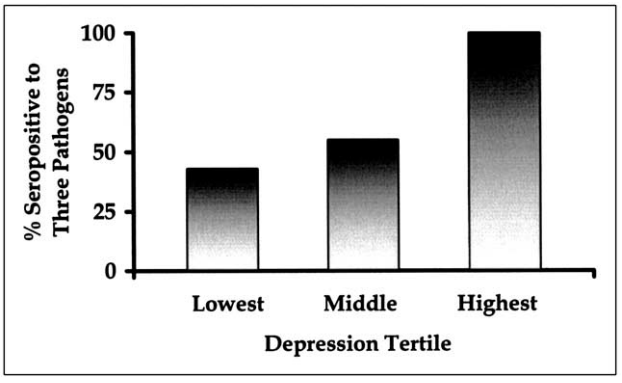

FIGURE 2. One hundred percent of patients in the highest tertile, i.e., those who had depressive symptoms of moderate severity, were seropositive to all 3 of the latent viruses assessed. This pattern was much less common among patients in the middle tertile (p = 0.001) and lowest tertile (p = 0.001), who reported depressive symptoms of mild and negligible severity, respectively.

= 0.41, p = 0.001). Further analyses showed that 100% of patients in the highest symptom tertile were seropositive to all 3 viruses (Figure 2). This pattern was much less common among patients in the middle tertile (55%; p = 0.001) and lowest tertile (43%; p = 0.001). In terms of pathogens (Figure 3), patients in the highest tertile were more likely to be seropositive for cytomegalovirus than were patients in the middle tertile (Kendall's τ_b, p = 0.008) and lowest tertile (p = 0.001). They also were more likely to be seropositive for herpes simplex virus than were patients in the lowest tertile (p = 0.005). The 3 groups were similar with respect to Epstein-Barr virus (p >0.30 for all groups). There were no disparities in pathogen burden according to the presence of clinical depression (p >0.10).

The clustering of pathogen burden and systemic inflammation confers a potent risk of morbidity and mortality.[19,20] To determine whether depressive symptoms are associated with this pattern, we classified patients as clustered if they were seropositive to all 3 viruses and had a CRP level ≥3.0 mg/L (the high-risk cutoff recommended by the American Heart Association and the Centers for Disease Control and Prevention).[21] Patients in the highest depression symptom tertile were significantly more likely to show clustering (i.e., evidence of pathogen burden and systemic inflammation) than did patients in the middle tertile (Kendall's τ_b, p = 0.001) or the lowest tertile (p = 0.002). The latter groups did not differ (p = 0.94). The percentages of patients who showed clustering were 62%, 19%, and 19% in the highest, middle, and lowest tertiles, respectively (Figure 4).

Despite its association with depressive symptoms, pathogen burden was unrelated to CRP expression (p = 0.62). When specific pathogens were considered, Epstein-Barr virus and herpes simplex virus were unrelated to CRP level (p > 0.23), but patients who showed positivity for cytomegalovirus had marginally higher CRP levels (p <0.08). Nevertheless, when pathogen seropositivity was statistically controlled, the association between depression and CRP level remained intact (p < 0.07). These findings indicate that latent infections underlie little (if any) of the excess CRP among patients who have high levels of depressive symptoms.

Ruling out alternative explanations: To evaluate alternative explanations for these findings, we reconducted analyses to control for potential confounders. Relations between depressive symptoms and biologic outcomes were independent of demographics, such as age, gender, ethnicity, and marital status (p <0.05). They also were independent of medical history (current smoker, obesity, sleep apnea, diabetes, hypertension, angina, myocardial infarction, congestive heart failure, atrial fibrillation, peripheral vascular disease, and stroke) and disease severity as indexed by Killip's class and time since infarction (p <0.04). Controlling for receipt of angioplasty, coronary bypass surgery,

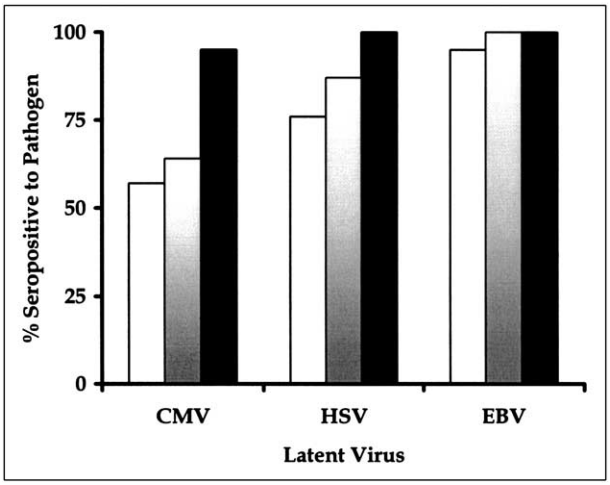

FIGURE 3. Patients in the highest tertile *(black bars)* of depression were more likely to be seropositive for cytomegalovirous (CMV) than were patients in the middle tertile *(gray bars)* (p = 0.008) and lowest tertile *(white bars)* (p = 0.001). They also were more likely to be seropositive for herpes simplex virus (HSV) than were patients in the lowest tertile (p = 0.005). The groups were similar in terms of Epstein-Barr (EBV) (p >0.30).

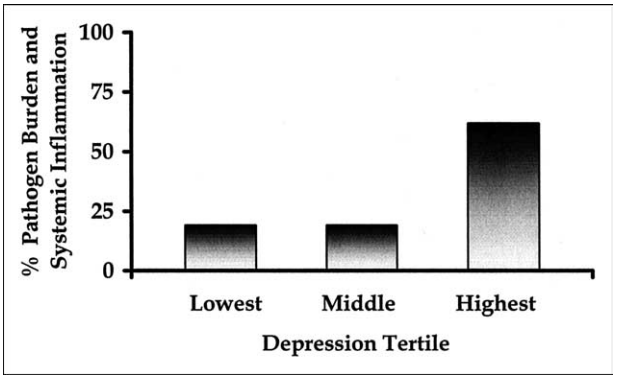

FIGURE 4. Patients were classified as showing clustering if they were seropositive to all 3 latent pathogens and had a CRP level ≥3.0 mg/L. Patients in highest symptom tertile were significantly more likely to show clustering than were patients in the middle tertile (p = 0.001) and lowest tertile (p = 0.002). The latter groups did not differ from each another (p = 0.94).

angiotensin-converting enzyme inhibitors, antiarrhythmic medication, antidepressants, anticoagulants, aspirin, β blockers, calcium channel blockers, diuretics, digitalis, nitrates, statins, and vasodilators did not attenuate the associations ($p < 0.05$). Collectively, these findings indicate that disparities in demographics or the extent, severity, and management of disease are responsible for little (if any) of the systemic inflammation or pathogen burden evident in patients who have depressive symptoms.

DISCUSSION

We found evidence of a graded relation between depressive symptoms and systemic inflammation in patients who were recovering from an ACS. Follow-up analyses showed that this association was strongest in patients who had depressive symptoms in the highest tertile. These patients had CRP levels >50% than did those in the middle or lowest tertile. This disparity was not simply a result of clinical depression because no association emerged between diagnosis and inflammation. Thus, high levels of depressive symptoms, regardless of where they are with respect to the diagnostic threshold, are associated with a marked increase in CRP. Although the clinical significance of this finding is unclear, CRP predicts mortality in a roughly dose-response fashion in patients who have cardiac disease.[22] Patients who have CRP levels ≥3.0 mg/L, like those in the highest tertile of depressive symptoms, represent a high-risk group for adverse cardiac outcomes.[21]

These findings contribute to a growing corpus of evidence that links depression with inflammation. In healthy adults there is a graded, linear relation between depressive symptoms and inflammatory molecules and evidence that clinical depression is accompanied by marked increases in CRP (41%) and interleukin-6 (54%).[23–25] Similar evidence is emerging in patients who have cardiac disease. One recent study of patients who had an ACS-associated major depression with increased levels of soluble intercellular adhesion molecule-1.[13] Another associated exhaustion, which is common in depression, with increased levels of interleukin-1β and tumor necrosis factor-α.[10] Collectively, these findings highlight inflammation as a potential mechanism that underlies the excessive morbidity and mortality in patients who have an ACS and depressive symptoms.

There also was evidence of a graded relation between depressive symptoms and pathogen burden. This effect was most evident among patients who had symptoms in the highest tertile and was independent of whether these patients met diagnostic criteria for clinical depression. The size of this effect was notable: 100% of patients in the highest symptom tertile were seropositive to all 3 viruses compared with only a few patients in the middle and lowest tertiles. These disparities in pathogen burden suggest another plausible mechanism that underlies the excessive morbidity and mortality among patients who have an ACS and depressive symptoms. Although the evidence linking infection with cardiac outcomes is mixed,[26] studies have suggested that pathogen burden, when coupled with systemic inflammation, confers a strong risk of morbidity and mortality.[19,20] Our findings suggest that these processes cluster in patients who have depressive symptoms. More than 60% of patients in the highest symptom tertile showed evidence of systemic inflammation and pathogen burden, whereas the comparable figure was 19% among patients in the other tertiles.

Although they reliably clustered in patients who had depressive symptoms, pathogen burden and CRP expression were unrelated in this sample, suggesting that latent infection does not act as an inflammatory stimulus. What else could underlie the depression–inflammation association? We examined the roles of smoking and adiposity, which promote inflammation, but they did not explain the high levels of CRP. These

findings are somewhat surprising because, in healthy young adults, adiposity explains most of the excessive CRP and interleukin-6 associated with depression.[23,27,28] We also examined whether medical history, disease severity, or management might underlie associations between depression and inflammation. Findings showed that disease characteristics do not simply foster a spurious association between these processes. Thus, the reason depressive symptoms become associated with CRP in patients who have an ACS is not clear, and it will be important for future research to identify the underlying mechanisms.

The cross-sectional design of this study precludes causal inferences regarding the associations between depression, pathogen burden, and inflammation. Because each of these processes is capable of eliciting the others,[11,29,30] it is tempting to speculate that patients enter a vicious positive-feedback circuit, the long-term result of which is increased vulnerability to morbidity and mortality from CAD. To evaluate this hypothesis, future studies will need to repeatedly assess depression, pathogen burden, and inflammation in a longitudinal protocol and determine their relations with clinical outcomes over time. This sort of work is likely to yield critical insights into the mechanisms through which depression contributes to morbidity and mortality from CAD.

1. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease. *Arch Gen Psychiatry* 1998;55:580–592.

2. Lesperance F, Frasure-Smith N, Talajic M. Major depression before and after myocardial infarction: its nature and consequences. *Psychosom Med* 1996;58: 99–110.

3. Rudisch B, Nemeroff CB. Epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 2003;54:227–240.

4. Lesperance F, Frasure-Smith N, Juneau M, Théroux P. Depression and 1-year prognosis in unstable angina. *Arch Intern Med* 2000;160:1354–1360.

5. Lesperance F, Frasure-Smith N, Talajic M, Bourassa MG. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. *Circulation* 2002;105:1049–1053.

6. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA* 1993;270:1819–1825.

7. Carney RM, Rich MW, Freedland KE, teVelde AJ, Saini J, Simeone C, Clark K. Major depressive disorder predicts cardiac events in patients with coronary artery disease. *Psychosom Med* 1988;50:627–633.

8. Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. *Am J Psychiatry* 1998;155:4–11.

9. Carney RM, Freedland KE, Miller GE, Jaffe AS. Depression as a risk factor for cardiac mortality and morbidity: a review of potential mechanisms. *J Psychosom Res* 2002;53:897–902.

10. Appels A, Bar FW, Bar J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. *Psychosom Med* 2000; 62:601–605.

11. Goodkin K, Appels A. Behavioral-neuroendocrine-immunologic interactions in myocardial infarction. *Med Hypoth* 1997;48:209–214.

12. Kop WJ, Cohen N. Psychological risk factors and immune system involvement in cardiovascular disease. In: Ader R, Felten D, Cohen N, eds. Psychoneuroimmunology. New York: Academic Press, 2001:525–544.

13. Lesperance F, Frasure-Smith N, Théroux P, Irwin M. The association between major depression and levels of soluble intercellular adhesion molecule-1, interleukin-6, and C-reactive protein in patients with recent acute coronary syndromes. *Am J Psychiatry* 2004;161:271–277.

14. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961;5:462–467.

15. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry* 1988;45:742–747.

16. Freedland KE, Skala JA, Carney RM, Raczynski JM, Taylor CB, Mendes de Leon CF, Ironson G, Youngblood ME, Krishnan KR, Veith RC. The Depression Interview and Structured Hamilton (DISH): rationale, development, characteristics, and clinical validity. *Psychosom Med* 2002;64:897–905.

17. Ridker PM, Rifai N, Pfeffer M, Sacks F, Lepage S, Braunwald E. Elevation of tumor necrosis factor-α and increased risk of recurrent coronary events after myocardial infarction. *Circulation* 2000;101:2149–2153.

18. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000;342:836–843.

19. Roivainen M, Viik-Kajander M, Palosuo T, Toivanen P, Leinonen M, Saikku P, Tenkanen L, Manninen V, Hovi T, Mänttäri M. Infections, inflammation and the risk of coronary heart disease. *Circulation* 2000;101:252–257.

20. Mayr M, Kiechl S, Willeit J, Wick G, Xu Q. Infections, immunity, and atherosclerosis. *Circulation* 2000;102:833–839.

21. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, Fadl YY, Fortmann SP, Hong Y, Myers GL, et al. Markers of inflammation and cardiovascular disease application to clinical and public health practice—a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 2003;107:499–511.

22. Blake GJ, Ridker PM. C-reactive protein and other inflammatory risk markers in acute coronary syndromes. *J Am Coll Cardiol* 2003;41:37S–42S.

23. Miller GE, Stetler CA, Carney RM, Freedland KE, Banks WA. Clinical depression and inflammatory risk markers for coronary heart disease. *Am J Cardiol* 2002;90:1279–1283.

24. Dentino AN, Pieper CF, Rao KMK, 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 Geriatric Soc* 1999;47:6–11.

25. Kop WJ, Gottdiener JS, Tangen CM, Fried LP, McBurnie MA, Walston J, Newman AB, Hirsch C, Tracy RP. Inflammatory and coagulation factors in persons >65 years of age with symptoms of depression but without evidence of myocardial ischemia. *Am J Cardiol* 2002;89:419–424.

26. Pahor M, Elam M, Garrison RJ, Kritchevsky SB, Applegate WB. Emerging noninvasive biochemical mesaures to predict cardiovascular risk. *Arch Intern Med* 1999;159:237–245.

27. Miller GE, Freedland KE, Carney R, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain Behav Immun* 2003;17:276–285.

28. Ladwig KH, Marten-Mittag B, Lowel H, Doring A, Koenig W. Influence of depressive mood on the association of CRP and obesity in 3205 middle aged healthy men. *Brain Behav Immun* 2003;17:268–275.

29. Maier SF, Watkins LR. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. *Psychol Rev* 1998;105:83–107.

30. Miller GE. How does stress get inside the body to influence depression? Some answers from the perspective of behavioral immunology. In: Barch DM, ed. Cognitive and Affective Neuroscience Approaches to Psychopathology. New York: Oxford University Press, in press.