Depression as a risk factor for cardiac mortality and morbidity
A review of potential mechanisms

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Abstract

Depression increases the risk of cardiac mortality and morbidity in patients with coronary heart disease (CHD), but the mechanisms that underlie this association remain unclear. This review considers the evidence for several behavioral and physiological mechanisms that might explain how depression increases the risk for incident coronary disease and for subsequent cardiac morbidity and mortality. The candidate mechanisms include: (1) antidepressant cardiotoxicity; (2) association of depression with cardiac risk factors such as cigarette smoking, hypertension, diabetes, and reduced functional capacity; (3) association of depression with greater coronary disease severity; (4) nonadherence to cardiac prevention and treatment regimens; (5) lower heart rate variability (HRV) reflecting altered cardiac autonomic tone; (6) increased platelet aggregation; and (7) inflammatory processes. Despite recent advances in our understanding of these potential mechanisms, further research is needed to determine how depression increases risk for cardiac morbidity and mortality. © 2002 Elsevier Science Inc. All rights reserved.

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Introduction

Comorbid depression is common in coronary heart disease (CHD). Approximately one in five patients with newly diagnosed coronary disease has major depression [1,2], and the prevalence is similar in patients recovering from an acute myocardial infarction (MI) [1,2]. Another one in five patients has minor depression at these times [1,3].

Depression is associated with increased risk for cardiac morbidity and mortality in patients with CHD, especially following acute MI [1,2]. For example, major depression is associated with a fourfold increase in the risk of mortality during the first 6 months following acute MI, after adjusting for covariates. Moreover, the prognostic significance of depression is comparable to that of left ventricular dysfunction and prior MI [4]. In initially disease-free cohorts, depression increases the risk for developing CHD [2].

The mechanisms underlying the relationship between depression and cardiac events are unclear. Their discovery may enable clinicians to identify the patients who are at the greatest risk and to intervene in the most harmful components of their depression. In an earlier paper, we offered several plausible behavioral and physiological explanations for the relationship between depression and cardiac morbidity and mortality [1]. Some of them (antidepressant cardiotoxicity, association with major cardiac risk factors, sedentary life style, and coronary disease severity) imply that the relationship may be spurious, i.e., that depression predicts but is not causally related to CHD morbidity or mortality. The other explanations (nonadherence to cardiac prevention and treatment regimens, and dysregulation of autonomic, neuroendocrine, and serotonergic systems) imply that depression may directly influence the course and outcome of CHD. Recent studies support some of these candidate mechanisms but not others.

Antidepressant cardiotoxicity

Certain antidepressants, especially tricyclics and monoamine oxidase inhibitors, have cardiotoxic side effects [5,6].

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The excess cardiac morbidity and mortality of comorbid depression might be due to its pharmacological treatment rather than to the depression itself [6]. However, antidepressant cardiotoxicity probably accounts for very little morbidity or mortality in depressed CHD patients. First, the association between depression and cardiac mortality was observed long before antidepressant medications were developed (e.g., Ref. [7]). Second, only a small proportion of cardiotoxic reactions to antidepressants are severe or life threatening [5]. Third, selective serotonin reuptake inhibitors (SSRIs) have few cardiotoxic side effects [8], and they currently are the frontline antidepressants for cardiac patients [8]. Finally, depression is seldom recognized in cardiac patients either by their cardiologists or by their primary care physicians [1]; frequently, antidepressants are not prescribed even when depression *is* recognized.

Major cardiac risk factors

Depression is associated with several of the major cardiac risk factors. Hypertension is more prevalent in depressed community residents [9], depressed medical patients [10], and depressed psychiatric patients [11] than in nondepressed controls. Depressed psychiatric patients are more likely to smoke cigarettes than are nondepressed controls and it is harder for them to quit [12]. The prevalence of smoking is higher in depressed than nondepressed CHD patients (e.g., Ref. [1]). Comorbid depression is common in diabetes, and the prevalence of diabetes is higher in depressed than nondepressed CHD patients (e.g., Ref. [13]). Studies correlating depression with serum cholesterol levels have generally produced conflicting results, with some finding higher total cholesterol levels in depressed patients (e.g., Ref. [14]), and others failing to find a difference (e.g., Ref. [15]). There is also evidence that depression is associated with reduced exercise capacity in CHD patients [16], and predicts physical decline in older, community-dwelling adults [17]. Conversely, declining physical activity predicts more depression symptoms [18].

If smoking, hypertension, diabetes, and reduced exercise capacity are more prevalent or more severe in depressed than in nondepressed patients, then depressed patients might be at increased risk for cardiac events not because of their depression, but instead because of these other risk factors. However, there are several reasons to doubt this possibility. First, some studies that have shown depression to predict cardiac events have failed to find associations between depression and these risk factors (e.g., Ref. [4]). Second, in studies in which significant associations *have* been found, depression has remained an independent predictor of cardiac morbidity and mortality after controlling for these risk factors (e.g., Refs. [19,20]). Third, there is reason to suspect that depression might *potentiate* other cardiac risk factors.

For example, diabetes is a risk factor for atherosclerosis, especially in women and African Americans, and it predicts a worse course in patients with identified CHD. Clouse et al. [21] interviewed a cohort of patients with Type 1 or Type 2 diabetes but without clinically manifest CHD, and followed them for 10 years. The depressed patients were about three times more likely to develop CHD over the course of the follow-up than were the nondepressed patients with diabetes, after controlling for traditional risk factors. These findings are similar to those reported by Kimberly et al. [22] in a large sample of Type 1 diabetic patients.

In another example of possible interactions between depression and traditional risk factors, Anda et al. [20] found that depressed affect and hopelessness were independent risk factors for CHD incidence and mortality among both smokers and nonsmokers. However, they also found that smoking was a more significant risk factor for CHD in patients with depressed mood or feelings of hopelessness.

These findings are similar to those of Kaplan et al. [23], who reported that the effect of smoking on the degree of carotid atherosclerosis in 1100 middle-aged men was 3.4 times greater in depressed compared to nondepressed men. They also found that the effect of LDL cholesterol level on atherosclerosis was nearly doubled, and the effect of fibrinogen level was nearly quadrupled in the depressed groups. Thus, although depression may be an independent risk factor for cardiac events, it also may potentiate the effects of other cardiac risk factors for reasons that are presently unclear.

In summary, it is difficult to dismiss the cardiac effects of depression as being due entirely to other, better established risk factors such as diabetes or smoking, although these risk factors may account for some of the observed effects of depression on cardiac endpoints. Furthermore, depression may potentiate the effects of other risk factors for cardiac events.

Coronary disease severity

Medical illnesses may lead to depression, and illnesses that have a poor prognosis may be more depressing than are less serious conditions. The roughly one in five patients who have comorbid major depression at various points in the course of CHD might also be the ones who have the most severe heart disease at these times. Thus, depressed cardiac patients might have worse medical outcomes than nondepressed patients simply because they have more severe CHD.

Depression does correlate with indices of the functional severity of heart disease such as New York Heart Association class, but not with physiological markers of heart disease severity such as left ventricular ejection fraction [24]. Across studies, there is no reliable relationship between depression and *any* physiological index of cardiac disease severity. Furthermore, the effects of depression on cardiac events are independent of the severity of coronary artery disease (CAD), the size of the MI (in post-MI

patients), the degree of left ventricular dysfunction, and most other well established indices of cardiac disease severity (e.g., Refs. [4,25]). Because there are a large number of risk factors and it is difficult to measure and adjust for more than a selected set of these in any given study, it remains possible that depression is related to an index of illness severity. Nevertheless, although coronary disease severity is an intuitively appealing explanation for the effects of depression in cardiac patients, and a popular one among those who dismiss the possibility that psychological factors might influence the course and outcome of chronic medical illnesses, there currently is very little evidence to support this point of view.

Recently, however, the cerebrovascular depression hypothesis has renewed interest in disease severity as a potential mechanism linking depression to CHD. If this hypothesis is correct, late onset depression is caused or exacerbated by cerebrovascular disease [26]. Since cerebrovascular comorbidity is common in elderly patients with advanced CHD, this again raises the possibility that cardiovascular disease severity explains depression's effects on CHD.

It is beyond the scope of this review to examine the vascular depression literature in depth. Briefly, while some studies have found structural or functional brain abnormalities in late onset depression (e.g., Ref. [27]), others have failed to detect them (e.g., Ref. [28]). Depression predicts cardiac morbidity and mortality independent of age, and there is evidence that the risk of cardiac mortality is higher in patients with early onset than with late onset depression [29]. Nevertheless, the possible association between cerebrovascular disease and late onset depression deserves more study.

Adherence to medical treatment regimens

Depression decreases patient adherence to medical treatments for many chronic illnesses [30]. Depressed CHD patients are less adherent to cardiac medication regimens [31], lifestyle risk factor interventions [32], and cardiac rehabilitation programs [33] than are nondepressed patients. For example, we found that in the first few weeks after coronary angiography, depressed patients over age 65 adhered to a prophylactic aspirin regimen on significantly fewer days than did nondepressed patients [31]. Aspirin, beta blockers, and other cardiac medications can reduce mortality in CHD patients, and failure to take these medications as prescribed can reduce their effectiveness. Thus, the extent to which poor adherence to medical treatment regimens accounts for the increased risk of mortality or morbidity in depressed patients remains an important area to study.

At least one study has provided evidence that patients with depression or other psychiatric disorders are less likely to receive the same level of care after MI as nondepressed patients [34], although the reasons for this are not clear. Further research is needed to replicate and explain these findings.

Altered cardiac autonomic tone

Neurohormonal dysregulation is one of the most plausible explanations for the effects of depression on medical morbidity and mortality in CHD patients [1,2]. Evidence of dysregulation of the autonomic nervous system (ANS) and of the hypothalamic–pituitary–adrenal (HPA) axis in medically well patients with major depressive disorder includes elevated plasma and urinary catecholamines and cortisol [1,2]. Decreased parasympathetic and increased sympathetic nervous system activity predisposes CHD patients to myocardial ischemia, ventricular tachycardia, ventricular fibrillation, and sudden cardiac death [1,2]. The ANS abnormalities associated with depression could therefore accelerate the progression of CAD and precipitate cardiac events by altering cardiac autonomic tone, promoting procoagulant and proinflammatory processes, lowering the threshold of mental stress-induced ischemia, and prolonging the QT interval.

Heart rate variability (HRV) analysis is an inexpensive, noninvasive technique for studying cardiac autonomic tone. Low HRV suggests excessive sympathetic and/or inadequate parasympathetic tone, and it is a powerful, independent predictor of mortality in patients with a recent MI [35,36] or with stable CAD [37]. There is growing evidence that it is lower in depressed than in medically comparable nondepressed patients with stable coronary disease [38–40] and in post-MI patients [13].

The prognostic importance of low HRV in depressed CHD patients has not yet been investigated. However, its potential clinical significance can be appreciated when the results of studies of depressed patients are compared to the results of relevant studies of HRV in large cohorts of patients with CHD. In a study of medically stable (i.e., cardiac event-free for at least 6 months) CHD patients [39], 47% of those who were moderately-to-severely depressed compared to 13% of those who were not depressed were below a level of very low frequency (VLF) power that was associated with a 4.4 relative risk of mortality in a group of comparable patients [36]. In a study of depressed post-MI patients [13], 7% of the nondepressed patients and 16% of the depressed patients had VLF power below a level that was associated with a 4.7 relative risk of mortality over a 2.5-year period in a larger study of post-MI patients [41]. This provides indirect evidence that low HRV might increase the risk of mortality in CHD patients.

Platelet reactivity

Plasma catecholamines increase platelet aggregation, lower the threshold for myocardial ischemia, and increase the risk of coronary thrombosis [42]. Platelet aggregation plays a critical role in MI, unstable angina, and in atherogenesis [42–44], and is increased in medically well depressed patients. For example, Musselman et al. [45]

found that depressed patients exhibited 41% greater platelet activation and responsiveness than did healthy, nondepressed subjects. There is at least limited evidence for this effect in depressed CHD patients. Laghrissi-Thode et al. [46] found higher plasma concentrations of platelet factor 4 (PF4) and β thromboglobulin (BTG), two proteins that are secreted from alpha granules when the platelet is activated, in depressed patients with CHD than in healthy, nondepressed individuals, and in nondepressed patients with CHD. They also found that these differences could be abolished by paroxetine [47]. This is very similar to the findings reported by Musselman et al. [48] of normalization of platelet activation in depressed patients following administration of paroxetine. Thus, platelet aggregation associated with depression may contribute to the process of atherogenesis as well as to the increased risk of cardiac events in depressed patients, especially in untreated cases.

Inflammatory processes

CAD is increasingly being viewed as a chronic inflammatory response to injuries of the vascular endothelium [49,50]. Depression may contribute to the onset of this process by triggering recurrent endothelial injuries. It could accomplish this by promoting maladaptive health practices such as cigarette smoking [51], triggering dysregulation of the neurohormonal systems responsible for cortisol and catecholamine secretion [52], or increasing susceptibility to infection with latent pathogens that colonize the vessel wall [53]. Each of these processes could damage the endothelium, thereby triggering inflammatory processes that contribute to the progression of atherosclerosis [50].

Depression may also contribute to the maintenance of inflammatory responses once they have been initiated. Depression is now viewed as a chronic illness with a relapsing course [54], and each new episode could contribute to endothelial injury. It is also possible that depression maintains inflammatory responses by diminishing the immune system's sensitivity to the glucocorticoid hormones that are responsible for terminating the inflammatory response. To the extent that depression promotes cortisol hypersecretion, leukocytes could down-regulate glucocorticoid receptor expression, and thereby increase resistance to cortisol's anti-inflammatory actions. A recent study found in vitro evidence of this phenomenon in adults suffering from chronic stress [55]. However, it has yet to be examined in the context of depression.

Very little is known about whether depression promotes inflammatory processes [56]. A number of studies have shown that in medically healthy adults, depression is accompanied by higher circulating levels of interleukin-6, C-reactive protein, and tumor necrosis factor-α [57,58], all of which are inflammatory risk markers for cardiac morbidity and mortality [59–61]. Although these findings are promising, their interpretation is complicated by the failure to account for potential confounders such as medications, cigarette smoking, acute infectious illnesses, and hospitalization status [51]. Much less attention has been paid to the link between depression and inflammation in patients with existing cardiac disease. A recent study in this area documented elevations in circulating interleukin-1β and tumor necrosis factor-α among patients with high levels of depressive symptoms and a related condition called vital exhaustion [62]. Interestingly, these patients also had elevated antibody titres to cytomegalovirus and *Chlamydia pneumoniae*, suggesting a potential pathway through which depression might contribute to the inflammatory process.

Conclusion

Since our first review was published in 1995, considerable progress has been made in mechanistic research on the association between depression and cardiac morbidity and mortality. In reviewing this literature, one is struck by the many plausible ways in which depression could have a negative effect on cardiac functioning and coronary disease. However, we still do not know which of the possibilities reviewed here, if any, explain this relationship. Furthermore, we know very little about how heart disease affects depression. This is also a very important and relatively neglected area for study. Finally, at present, it is not known whether treating depression will reduce the risk of cardiac mortality or morbidity. However, depression is associated with significant psychological, social, and physical disability, independent of other chronic medical illnesses [63]. Effective treatment of depression has been shown to enhance quality of life and improve overall functioning in these patients [63]. Thus, we strongly recommend that the identification and treatment of depression in patients with cardiac disease be made a part of routine care.

Acknowledgments

References

[1] Carney RM, Freedland KE, Rich MW, Jaffe AS. Depression as a risk factor for cardiac events in established coronary heart disease: a review of possible mechanisms. Ann Behav Med 1995;17:142–9.

[2] Glassman AH, Shapiro PA. Depression and the course of coronary artery disease. Am J Psychiatry 1998;155:4–111.

[3] Schleifer SJ, Macari-Hinson MM, Coyle DA, Slater WR, Kahn M, Gorlin R, Zucker HD. The nature and course of depression following myocardial infarction. Arch Intern Med 1989;149:1785–9.

[4] Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction: impact on 6 month survival. J Am Med Assoc 1993;270:1819–25.

[5] Glassman AH, Roose SP, Bigger JT. The safety of tricyclic antidepressants in cardiac patients. Risk–benefit considered. J Am Med Assoc 1993;269:2673–5.

[6] Cohen HW, Gibson G, Alderman MH. Excess risk of myocardial infarction in patients treated with antidepressant medications: association of use of tricyclic agents. Am J Med 2000;108:2–8.

[7] Fuller RG. What happens to mental patients after discharge from hospital? Psychiatry Q 1935;9:95–104.

[8] Sheline Y, Freedland KE, Carney RM. How safe are serotonin reuptake inhibitors for depression in patients with coronary heart disease? Am J Med 1997;102:54–9.

[9] Wells KB, Golding JM, Burnam MA. Affective, substance use, and anxiety disorders in persons with arthritis, diabetes, heart disease, high blood pressure, or chronic lung conditions. Gen Hosp Psychiatry 1989;11:320–7.

[10] Wells KB, Rogers W, Burnam A, Greenfield S, Ware JE. How the medical comorbidity of depressed patients differs across health care setttings: results from the Medical Outcomes Study. Am J Psychiatry 1991;148:1688–96.

[11] Pfohl B, Rederer M, Coryell W, Stangl D. Association between post dexamethasone cortisol level and blood pressure in depressed inpatients. J Nerv Ment Dis 1991;179:44–7.

[12] Glassman AH, Helzer JE, Covey LS, Cottler LB, Stetner F, Tipp JE, Johnson J. Smoking, smoking cessation, and major depression. J Am Med Assoc 1990;264:1546–9.

[13] Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF, Czajkowski SM, O'Connor C, Stone PH, Freedland KE. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001;104:2024–8.

[14] Oxenkrug GF, Branconnier RJ, Harto-Truax N, Cole JO. Is serum cholesterol a biological marker for major depressive disorder? Am J Psychiatry 1983;40:920–1.

[15] Bajwa WK, Asnis GM, Sanderson WC, Irfan A, van Praag HM. High cholesterol levels in patients with panic disorder. Am J Psychiatry 1992;149:376–8.

[16] Milani RV, Lavie CJ, Cassidy MM. Effects of cardiac rehabilitation and exercise training programs on depression in patients after major coronary events. Am Heart J 1996;132:726–32.

[17] Penninx BWJH, Guralnik JM, Ferrucci L, Simonsick EM, Deeg DJH, Wallace RB. Depressive symptoms and physical decline in community dwelling older persons. J Am Med Assoc 1998;279:172–1726.

[18] Lampinen P, Heikkinen RL, Ruoppila I. Changes in intensity of physical exercise as predictors of depressive symptoms among older adults: an eight year follow up. Prev Med 2000;30:371–80.

[19] Hippisley-Cox J, Fielding K, Pringle M. Depression as a risk factor for ischaemic heart disease in men: population based case–control study. Br Med J 1998;316:1714–9.

[20] Anda R, Williamson D, Jones D, Macera C, Eaker E, Glassman A, Marks J. Depressed affect, hopelessness, and the risk of ischemic heart disease in a cohort of U.S. adults. Epidemiology 1993;4:285–94.

[21] Clouse RE, Freedland KE, Carney RM, Griffith P, Lustman PJ. Depression accelerates the presentation of coronary heart disease in women with diabetes mellitus. Psychosom Med 2001;63:103.

[22] Kimberly Y, Forrest Z, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower extremity arterial disease in type 1 diabetes the same? Atherosclerosis 2000;148:159–69.

[23] Kaplan GA, Cohen RD, Wilson TW, Kauhanen J, Salonen JT, Salonen R. Depression amplifies the association between carotid atherosclerosis and age, hypertension, low density lipoproteins, and platelet aggregability. 32nd Annual Conference on Cardiovascular Disease Epidemiology. Dallas (TX): American Heart Association Press, 1992 March 19–21.

[24] Skala JA, Freedland KE, Carney RM. Depressive symptoms and functional status in patients with congestive heart failure. Ann Behav Med 1995;17:S134.

[25] Carney RM, Rich MW, Freedland KE, te Velde A, Saini J, Simeone C, Clark K. Major depressive disorder predicts cardiac events in patients with coronary artery disease. Psychosom Med 1988;50:627–33.

[26] Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. Vascular depression hypothesis. Arch Gen Psychiatry 1997;54:915–22.

[27] Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry 1997;154:497–501.

[28] Greenwald BS, Kramer-Ginsberg E, Krishnan DRR, Ashtari M, Aupperle PM, Patel M. MRI signal hyperintensities in geriatric depression. Am J Psychiatry 1996;153:1212–5.

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

[30] DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment. Arch Intern Med 2000;160:2101–7.

[31] Carney RM, Freedland KE, Eisen S, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol 1995;14:88–90.

[32] Ziegelstein RC, Fauerbach JA, Stevens SS, Romanelli J, Richter DP, Bush DE. Patients with depression are less likely to follow recommendations to reduce cardiac risk during recovery from a myocardial infarction. Arch Intern Med 2000;160:1818–23.

[33] Blumenthal JA, Williams RS, Wallace AG, Williams RB, Needles TL. Physiological and psychological variables predict compliance to prescribed exercise therapy in patients recovering from myocardial infarction. Psychosom Med 1982;44:519–27.

[34] Druss BG, Bradford DW, Rosenheck RA, Radford MJ, Krumholz HM. Mental disorders and use of cardiovascular procedures after myocardial infarction. J Am Med Assoc 2000;283:506–11.

[35] Kleiger RE, Miller JP, Bigger JT, Moss AJ, Multicenter Post-Infarction Research Group. Decreased heart rate variability and its association with mortality after myocardial infarction. Am J Cardiol 1987;113:256–62.

[36] Bigger JT, Fleiss JL, Steinman RC, Rolnitzky LM, Kleiger RE, Rottman JN. Frequency domain measures of heart period variability and mortality after myocardial infarction. Circulation 1992;85:164–71.

[37] Rich MW, Saini JS, Kleiger RE, Carney RM, te Velde A, Freedland KE. Correlation of heart rate variability with clinical and angiographic variables and late mortality after coronary angiography. Am J Cardiol 1988;62:714–7.

[38] Carney RM, Saunders RD, Freedland KE, Stein P, Rich MW, Jaffe AS. Depression is associated with reduced heart rate variability in patients with coronary heart disease. Am J Cardiol 1995;76:562–4.

[39] Stein PE, Carney RM, Freedland KE, Skala JA, Kleiger RE, Rottman JN, Jaffe AS. Severe depression is associated with markedly reduced heart rate variability in patients with stable coronary heart disease. J Psychosom Res 2000;48:493–500.

[40] Krittayaphong R, Cascio WE, Light KC, Sheffield D, Golden RN, Finkel JB, Glekas G, Koch GG, Sheps DS. Heart rate variability in patients with coronary artery disease: differences in patients with higher and lower depression scores. Psychosom Med 1997;59:231–5.

[41] Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC. Frequency domain measures of heart period variability to assess risk late after myocardial infarction. J Am Coll Cardiol 1993;21:729–36.

[42] Markovitz JH, Matthews KA. Platelets and coronary heart disease: potential psychophysiologic mechanisms. Psychosom Med 1991;53:643–68.

[43] Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. N Engl J Med 1986;315:983–9.

[44] Trip MD, Cats VM, van Capelle FJL, Vreeken J. Platelet hyperactivity and prognosis in survivors of myocardial infarction. N Engl J Med 1990;322:1549–54.

[45] Musselman DL, Tomer A, Manatunga AK, Knight BT, Porter MR,

de Baets M, Marzec U, Harker LA, Nemeroff CB. Exaggerated platelet reactivity in major depression. Am J Psychiatry 1996;153:1212–7.

[46] Laghrissi-Thode F, Wagner WR, Pollock BG, Johnson PC, Finkel MS. Elevated platelet factor 4 and β-thromboglobulin plasma levels in depressed patients with ischemic heart disease. Biol Psychiatry 1997;42(4):290–5.

[47] Pollock BG, Laghrissi-Thode F, Wagner WR. Evaluation of platelet activation in depressed patients with ischemic heart disease after paroxetine or nortriptyline treatment. J Clin Psychopharmacol 2000; 20(2):137–40.

[48] Musselman DL, Marzec UM, Manatunga A, Penna S, Reemsnyder A, Knight BT, Baron A, Hanson SR, Nemeroff CB. Platelet reactivity in depressed patients treated with paroxetine: preliminary findings. Arch Gen Psychiatry 2000;57:875–82.

[49] Berliner A, Navab M, Fogelman AM, Frank JS, Demer LL, Edwards PA, Watson AD, Lusis AJ. Atherosclerosis: basic mechanisms. Circulation 1995;91:2488–96.

[50] Ross R. Atherosclerosis—an inflammatory disease. N Engl J Med 1999;340:115–26.

[51] Miller GE, Cohen S, Herbert TB. Pathways linking major depression and immunity in ambulatory female patients. Psychosom Med 1999; 61:850–60.

[52] Plotsky PM, Owens MJ, Nemeroff CB. Neuropeptide alterations in mood disorders. In: Bloom FE, Kupfer DJ, editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, 1995. pp. 971–81.

[53] Herbert TB, Cohen S. Depression and immunity: a meta-analytic review. Psychol Bull 1993;113:472–86.

[54] Judd LL. Pleomorphic expressions of unipolar depressive disease: summary of the 1996 CINP President's Workshop. J Affective Disord 1997;45:109–16.

[55] Miller GE, Cohen S, Ritchey AK. Chronic psychological stress and the regulation of pro-inflammatory cytokines: a Glucocorticoid Resistance Model. Manuscript submitted for publication.

[56] Kop WJ, Cohen N. Psychological risk factors and immune system involvement in cardiovascular disease. In: Ader R, Felten D, Cohen N, editors. Psychoneuroimmunology. New York: Academic Press, 2001. pp. 525–44.

[57] 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 Geriatr Soc 1999;47:6–11.

[58] Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. Cytokine 1997;9:853–8.

[59] Danesh J, Collins R, Appleby P, Peto R. Fibrinogen, C-reactive protein, albumin, and white cell count: meta-analyses of prospective studies of coronary heart disease. J Am Med Assoc 2000;279: 1477–82.

[60] 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.

[61] 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: 2149–53.

[62] Appels A, Bar FW, Bar J, Bruggeman C, de Baets M. Inflammation, depressive symptomatology, and coronary artery disease. Psychosom Med 2000;62:601–5.

[63] Ormel J, Von Korff M. Synchrony of change in depression and disability. Arch Gen Psychiatry 2000;57:381–2.