FRANÇOIS LESPÉRANCE, MD*
Centre Hospitalier de l'Université de Montréal
Montréal Heart Institute
Montréal, Québec, Canada

NANCY FRASURE-SMITH, PhD*
McGill University
Montréal Heart Institute
Centre Hospitalier de l'Université de Montréal
Montréal, Québec, Canada

Depression and heart disease

Considerable evidence strongly supports an association between depression and cardiac disease: depression (both major depressive disorder and depressive symptoms) is a predictor of short-term and long-term mortality in patients following myocardial infarction (MI) and is also a predictor of having an acute coronary event in the general population.

The nature of the association has been contested. Does depression cause heart disease because of behavioral factors, autonomic dysfunction, or enhanced inflammation? Or does another factor—such as dietary intake of foods rich in omega-3 fatty acids—simultaneously affect both depression and heart disease? Evidence supports each theory.

Despite the well-proven association between heart disease and depression, attempts thus far to target depression to improve heart disease outcomes have been unsuccessful.

This article reviews the strength of the epidemiologic data linking depression and heart disease and discusses possible mechanisms to explain this relationship.

DEPRESSION AS A RISK FACTOR FOLLOWING MI

There is much epidemiologic evidence to support an association between depression and increased mortality following MI.

In 1993, we followed 222 patients for 6 months after an MI and found that major depression was a significant predictor of mortality.[1]

A follow-up study[2] with 896 patients showed that the increased risk was not restricted only to those with major depression. The level of depression symptoms during admission, as assessed by the Beck Depression Inventory (BDI), had a dose-response relationship with cardiac mortality **(Figure 1)**. Even patients with only low levels of depressive symptoms at baseline had an increased risk of cardiac mortality over 5 years of follow-up. The risk associated with depression symptoms was independent and of about the same magnitude as having a previous MI, or having diabetes or ventricular dysfunction.

Welin et al[3] followed 275 patients younger than 65 years old who experienced a first MI and found that the increased risk of mortality associated with baseline depression was still evident for up to 9 years.

DEPRESSION AS A RISK FACTOR FOR A CARDIAC EVENT

Depression is also a risk factor for an incident cardiac event among initially healthy people. Rugulies[4] evaluated 11 cohort studies that assessed depression and coronary heart disease and found that people with clinical depression had more than 2.5 times the risk of an MI or coronary death as the general population. Those with symptoms of depression who did not meet the criteria for a diagnosis of clinical depression had about 1.5 times the chance of a future cardiac event.

HOW MIGHT DEPRESSION AFFECT HEART DISEASE?

Several plausible pathways could link depression with cardiac disease. Whether depression is actually the cause of, a consequence of, or only coincidentally associated with cardiac disease is still uncertain.

Risky behaviors. Depression may adversely influence behavioral factors, such as smoking, diet, exercise, and compliance with medical care, increasing the risk of cardiac mortality.

Autonomic function. Depression may enhance sympathetic nervous system activity, leading to increased cardiac mortality. Carney et al[5] found that patients with depression following an acute MI had greater autonomic dysfunction, as measured by heart rate variability indices, than patients after MI without depression.

Consequence model: Inflammation

Alternatively, atherosclerosis or MI may induce physiologic changes that cause depression. Atherosclerosis is associated with a subchronic elevation of cytokines, whereas acute MI triggers a more intense rise. These peripheral cytokines induce production of cytokines

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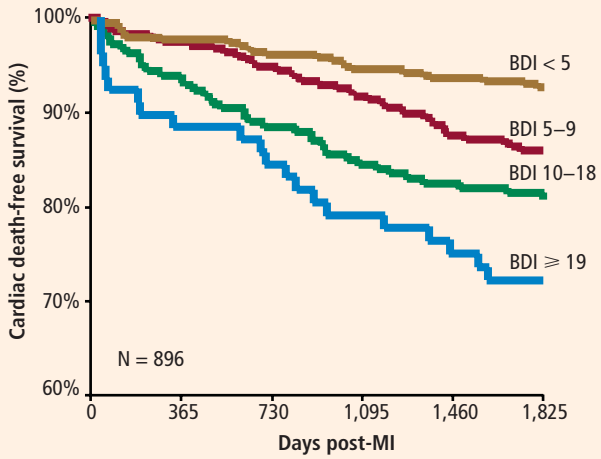

FIGURE 1. A dose-response relationship between depressive symptoms, as measured by scores on the Beck Depression Inventory (BDI), and long-term prognosis following myocardial infarction (MI) was evident in this study of post-MI patients who were followed for at least 5 years. Reprinted, with permission, from Lespérance et al. Five-year risk of cardiac mortality in relation to initial severity and one-year changes in depression symptoms after myocardial infarction. Circulation 2002 (Mar 5); 105:1049–1053.

TABLE 1
Relationships between depression and markers of inflammation among post-ACS patients

Inflammatory marker	BDI-II < 14 (n = 450)	BDI-II ⩾ 14 (n = 152)	*P*
Soluble intercellular adhesion molecule 1 (ng/mL)	179.1 (156.5–210.2)	192.6 (166.9–233.3)	.001
Interleukin-6 (pg/mL)	2.03 (1.41–3.14)	2.22 (1.41–3.64)	.30
C-reactive protein (mg/L)	1.66 (0.91–3.87)	2.02 (1.02–4.91)	.042

Levels of inflammatory markers expressed as median levels; numbers in parentheses represent the 25th and 75th percentiles.

ACS = acute coronary syndrome; BDI-II = Beck Depression Inventory II

Adapted from Frasure-Smith et al. Depression, C-reactive protein and two-year major adverse cardiac events in men after acute coronary syndromes. Biol Psychiatry 2006; vol. 60. In press. Copyright 2006, with permission from the Society of Biological Psychiatry.

in the brain, which then activates the hypothalamic-pituitary axis and the stress response and inhibits serotonin activity. This activation leads to "sickness behavior," such as is exhibited with the occurrence of an upper respiratory viral infection.[6]

Evidence indicates that MI may cause physical changes in the brain that cause depression, which is mediated by an inflammatory response.

Wann and colleagues[7,8] developed a rat model of post-MI depression. They found that 14 days after having an acute MI, rats showed behavioral changes consistent with depression (ie, reduced sucrose intake [an equivalent to anhedonia] and reduced performance on the forced swim test [an equivalent to behavioral despair]). In addition, these behavioral changes were associated with the presence of apoptosis in the prefrontal cortex, hypothalamus, and amygdala, a phenomenon that was suppressed by treating rats with pentoxifylline, an inhibitor of cytokine synthesis, or antidepressants.

Tyring et al,[9] in a randomized controlled study involving 618 patients with psoriasis, found that those taking etanercept, an inhibitor of the inflammatory marker tumor necrosis factor (TNF)-alpha, had improvements in scores measuring fatigue and depression. Improved scores did not completely correlate with improved joint pain and skin clearance. It is possible that the anti-inflammatory effects of the medication directly improved sickness behaviors.

At the Montreal Heart Institute, we evaluated the association between depression and inflammatory markers (soluble intercellular adhesion molecule 1 [sICAM-1], interleukin-6 [IL-6], and C-reactive protein [CRP]) in 602 men 2 months after hospitalization for an acute coronary syndrome.[10] Levels of sICAM-1 and CRP were significantly higher in men with depression **(Table 1)**. Two-year follow-up showed that the impacts of depression and CRP on major cardiac events were not additive (ie, that depression and CRP appear to be overlapping risk factors).[11]

Depression and inflammatory markers are also associated in people without known cardiac disease. Penninx et al[12] evaluated a community-based sample of well-functioning people aged 70 to 79 years and found that those with depressed mood had higher median plasma levels of IL-6, TNF-alpha, and CRP.

It is impossible to know at this point whether the link between heart disease, inflammation, and depression is unidirectional or bidirectional: each factor may give rise to the other.

Coincidence model: Omega-3 fatty acids

Evidence suggests that depression is linked to a worse prognosis in acute coronary syndromes by several mechanisms:

- Autonomic dysregulation, as shown by decreased heart rate variability and increased risk of ventricular arrhythmias

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- Platelet changes
- Inflammation
- Endothelial function.

It is possible that dietary factors affect both depression and heart disease through these mechanisms. One such potential dietary factor is omega-3 fatty acids.

Omega-3 and omega-6 fatty acids are polyunsaturated fatty acids that are so named because of the position of the first double bond on their carbon atom chain. Their molecular structure determines their three-dimensional configuration and biological properties. Arachidonic acid (an omega-6 fatty acid) and eicosapentaenoic acid (an omega-3 fatty acid) are both 20-carbon polyunsaturated fatty acids that are included in multiple biologic molecules such as prostaglandins and leukotrienes and have different physiologic actions.[13]

Omega-3 fatty acids are found in flax seed, canola, nuts, and fish. Eating more fish may improve prognosis in acute coronary syndromes by increasing heart rate variability and by antiarrhythmic, antithrombogenic, and anti-inflammatory actions. Increasing dietary consumption of omega-3 fatty acids also promotes nitric oxide-induced endothelial relaxation.

The GISSI-Prevenzione trial[14] randomized 11,324 post-MI patients to daily supplementation with either omega-3 fatty acids (1 g), vitamin E (300 mg), both, or neither for 3.5 years. Omega-3 fatty acid supplementation significantly reduced the combined incidence of death, nonfatal MI, and stroke compared with controls, whereas vitamin E supplementation had no effect.

Hibbeln[15] found an inverse relationship between average per capita annual fish consumption and the prevalence of major depression in nine countries. Other studies have also found an association between omega-3 fatty acid consumption and postpartum depression[16,17] or bipolar disorders.[18]

In a case-control study of patients recovering from an acute coronary syndrome, we found that depressed patients had significantly lower concentrations of omega-3 fatty acids than their nondepressed counterparts **(Table 2)**.[19]

TABLE 2
Relative levels of fatty acids between depressed cases and controls with recent acute coronary syndrome

	Age- and sex-matched controls (n = 54)	Depressed cases (n = 54)	*P*
Alpha linolenic acid *18:3n-3*	0.25 ± 0.08	0.25 ± 0.09	.71
Eicosapentaenoic acid (EPA) *20:5n-3*	1.20 ± 0.51	1.14 ± 0.58	.38
Docosahexaenoic acid (DHA) *22:6n-3*	3.85 ± 1.13	3.32 ± 1.03	.013
Total EPA and DHA	5.05 ± 1.44	4.46 ± 1.32	.024
Omega-3 total	6.63 ± 1.47	6.09 ± 1.43	.044
Omega-6 total	33.28 ± 1.60	33.50 ± 2.29	.57
Omega-6/omega-3 ratio	5.28 ± 1.27	5.84 ± 1.57	.044
Arachidonic acid (AA)/EPA ratio	10.46 ± 3.64	12.63 ± 6.63	.044
AA/DHA ratio	3.14 ± 1.05	3.88 ± 1.40	.002

Adapted from reference 19.

TREATING DEPRESSION TO REDUCE CARDIOVASCULAR RISK

No secondary prevention trial has successfully reduced cardiovascular risk by targeting depression.

The Enhancing Recovery in Coronary Heart Disease (ENRICHD) study[20] was a multicenter clinical trial involving 2,481 patients following an acute MI who were either depressed or had low social support. Patients were randomized to either 16 weeks of cognitive behavior therapy supplemented by treatment with a selective serotonin reuptake inhibitor (SSRI) or usual care. After 3.5 years, no difference was detected in survival rates between the two groups.[21] However, physicians of usual care patients were informed that their patients were depressed, and by the end of the trial a good proportion of the usual care patients had been treated with SSRI antidepressants. Thus, it is difficult to know if treating depression has no effect on cardiovascular risk or whether the intervention chosen for this trial was inadequate.

The Sertraline Antidepressant Heart Attack Trial (SADHART)[22] was a randomized controlled trial that tested the safety and efficacy of the SSRI antidepressant sertraline in 369 patients with major depression hospitalized for acute MI or unstable angina. Sertraline was found to be safe and mildly to moderately effective for treating depression in this population, but the incidence of serious adverse cardiac events and changes in surrogate cardiac markers were not significantly different between the treated and untreated groups.

The Canadian Cardiac Randomized Evaluation of

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Antidepressant and Psychotherapy Efficacy (CREATE),[23] evaluating the SSRI citalopram and interpersonal psychotherapy for treating major depression in patients with coronary artery disease, has just been completed. Results will be forthcoming.

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Address: *François Lespérance, MD, Department of Psychiatry, 1560 Sherbrooke E, M-3234, Montréal, Québec H2L 4M1, Canada; francois.lesperance@umontreal.ca.*

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