Heart disease and depression often go hand in hand. Shared biochemical similarities between the two conditions suggest that common treatment strategies may address both illnesses. Here we provide a primer on nutritional supplements that may help navigate the complex interplay of these two major health issues.

Heart disease and clinical depression present with different symptoms and are conventionally managed with different treatments. While heart disease can be acutely life threatening, depression tends to be slow and insidious. How can the seemingly unrelated conditions of heart disease and depression possibly be related?

Emerging research indicates that the deeper we probe, the more alike the two disorders appear to be. While the ultimate manifestations of heart disease and depression differ, the underlying biochemical pathologies are surprisingly similar. Beneath the emotional surface of mood and depression can be a raging physical undercurrent of hormonal distortions, impaired immunity, and inflammation. These disturbances of physiology contribute to the growth and abnormal activity of coronary plaque, eventually leading to heart attack. Depressed people, in fact, suffer a fourfold greater risk of heart attack compared to non-depressed people.1,2

If the two seemingly disparate disorders of depression and coronary heart disease share common causes, can there also be common treatments? Exciting new insights suggest that strategies to address both conditions do exist. These therapies work by treating the shared metabolic origins of heart disease and depression. The good news is that some of these treatments are powerful nutritional therapeutics, readily available to all. > > >
Depression:
More than a Feeling

Everyone has had the experience of feeling sad or blue. How do these everyday feelings differ from clinical depression? Symptoms of depression include loss of interest in activities previously enjoyed, struggling to sleep or awakening early, difficulty concentrating, feelings of worthlessness or guilt, loss of appetite or weight, and suicidal thoughts. Symptoms that interfere with daily activities and that last longer than two weeks may signal clinical depression.

Far more than just a state of mind involving sadness or hopelessness, depression is a disease in the true organic sense, with measurable symptoms. In the last decade, clinical investigations have uncovered the myriad physical manifestations of depression. Until recently, these manifestations have been little understood, but growing evidence asserts that they have very real consequences.

Feeling good can hinge on a precarious balance of internal dialogue and external events. This balance can easily tip, setting the stage for negative emotions and the resulting metabolic consequences. At what point do negative emotions begin to add to risk for heart disease?

The line that separates depression from the more commonplace feelings of sadness and anger that are part of all our lives can be somewhat hazy. It is a matter of the degree and duration of symptoms.

Full-blown depression is not necessary to increase heart disease risk, as even moderate feelings of hopelessness and sadness can more than double the risk of heart attack. People who chronically experience negative emotions—such as unexpressed anger, hostility, and resentment—also have a higher risk for heart attack. They experience a level of risk similar to that of the fully depressed.

Metabolic Underpinnings of Depression

Beneath the surface of sadness and hopelessness blazes an inferno of metabolic phenomena. Increased levels of inflammatory proteins, such as interleukin one-beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), circulate in the blood, suggesting that low-grade, body-wide inflammation accompanies depression. IL-1β and TNF-α levels correlate with the severity of depression, with higher levels of inflammatory proteins linked to more serious depression. C-reactive protein is another inflammatory protein found at higher levels in depressed persons. All these inflammatory mediators have been clearly linked to increased risk of heart attack. Extensive clinical trial data show that when the fires of inflammation are burning, coronary plaque is unstable and more prone to "rupture," an event that can lead to heart attacks. (See also "Quenching the Flames of Inflammation" and "The Fires Within," Life Extension, July 2004.)

Just as a life-threatening event such as a car accident triggers biochemical reactions in the body, depression activates the release of stress hormones. The feelings of anger, frustration, hostility, and anxiety are also associated with increased levels of stress hormones. Hypersecretion of corticotrophin-releasing hormone from the hypothalamus triggers the release of cortisol and norepinephrine, both of which are involved in the survival response that occurs when the human organism is threatened. These hormones are potent contributors to hypertension, insulin resistance, and
diabetes, three well-established risks for coronary disease. When negative emotions become chronic and deeply rooted, the risk for developing pathological heart disease grows.

Cortisol and norepinephrine also contribute to development of metabolic syndrome, a combination of abdominal obesity, hypertension, low high-density lipoprotein (HDL), and higher blood sugar (above 110 mg/dL). The epidemic numbers of overweight and obese people in America are fueling a skyrocketing increase in metabolic syndrome, estimated to currently affect 47 million US adults. Metabolic syndrome is a rapidly growing cause of heart disease, and depressed people are particularly prone to develop the features of metabolic syndrome.

During periods of depression, the “fight-or-flight” response of the sympathetic nervous system operates in a continuous state of heightened activation, releasing stress hormones into the bloodstream. The calming parasympathetic system is simultaneously suppressed. This reaction can be measured as blunted, beat-to-beat variation in heart rate, or heart-rate variability, even when the heart rate is normal. Decreased heart-rate variability predicts heightened potential for dangerous heart (ventricular) arrhythmias and sudden death.

For years, epidemiologists have explored the unexpectedly low risk of both heart disease and depression in cultures in which fish is eaten in abundant quantities. The common thread seems to be the high content of omega-3 fatty acids in fish oils. Through his studies across numerous cultures, Dr. Joseph Hibbeln of the National Institutes of Health has documented the remarkable association between higher levels of fish consumption and lower rates of depression. He was also among the first to draw the connection between greater fish consumption and the lower likelihood of heart attack.

Indeed, both depression and heart disease are associated with low concentrations of omega-3 fatty acids in red blood cells. Conventional prescription antidepressant medication fails to correct an imbalance of omega-3 fatty acids. It is tempting to suggest that supplementation with fish oil rich in omega-3 fatty acids might provide a common therapy for both depression and heart disease.

Research discussed later in this article suggests that it does. Homocysteine represents another intriguing connection between depression and heart disease. Homocysteine, an amino acid associated with the deficiency of certain B vitamins, has been clearly and conclusively associated with increased risk of heart attack. Less well known is homocysteine's role in emotions. Depression, poor response to antidepressant medication, and dysthymia (a lesser form of depression) have all been linked to low blood levels of folic acid. Folic acid deficiency causes high homocysteine blood levels. Folate-deficient people are also more likely to be deeply depressed and for longer periods. Up to 50% of depressed people have homocysteine levels that are significantly above normal, considered to be greater than 10 micromoles per liter (mmol/L) of blood. This variety of depression responds poorly to antidepressant medication, but does respond to folic acid. Studies examining depressed people in a number of settings have firmly established that folic acid replacement, resulting in reduced homocysteine blood levels, is an effective treatment for depression and a useful addition to prescription antidepressant therapies.

Depression and feelings of anger, hostility, and anxiety share several biochemical traits that are similar to those that form the foundations of risk for heart disease. These include a tendency toward inflammation, increased levels of stress hormones, the presence of metabolic syndrome, blunted heart-rate variability, reduced levels of omega-3 fatty acids, and elevated homocysteine levels. Nutritional supplements may be powerful tools in managing the overlapping syndromes of depression and heart disease.

<table>
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<tr>
<th>BIOCHEMICAL SIMILARITIES OF HEART DISEASE AND DEPRESSION</th>
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<tr>
<td>The common ground between coronary artery disease and depression is substantial. Consider that both states share:</td>
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<tr>
<td><strong>HEART DISEASE</strong></td>
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<tr>
<td>Inflammatory cytokines (TNF-α, IL-1, IL-2)</td>
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<td>Omega-3 fatty acids</td>
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<td>Homocysteine</td>
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<td>Folic acid</td>
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<td>Metabolic syndrome (abdominal fat, hypertension, low HDL, increased blood sugar)</td>
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<td>Stress hormones (cortisol, norepinephrine)</td>
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The Omega-3 Connection

Fish oil, containing abundant quantities of the omega-3 fatty acids docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), is a dual-action supplement with compelling data to support its use for both depression and heart disease. Some have called omega-3 fatty acids the “missing link” between the two disorders.

The human brain contains an extraordinarily high concentration of omega-3 fatty acids. This simple fact has prompted extensive investigation of the role of essential fats in various brain functions and diseases. A deficiency of omega-3 fatty acids has been associated with conditions as diverse as hostility, cognitive decline with aging, and attention-deficit/hyperactivity disorder.24 Several studies have demonstrated that people suffering from major depression are measurably deficient in omega-3 fatty acids.25-27 Not surprisingly, these and other studies have highlighted the failure of conventional antidepressant medication to correct the omega-3 deficiency.28 From an epidemiological viewpoint, cultures marked by abundant fish consumption and omega-3 intake, such as Eskimos and some of the coastal natives of Japan and Canada, are far less likely to suffer from depression than Americans. Conversely, cultures consuming less fish than Americans, such as New Zealanders, suffer substantially higher rates of depression.29-31

An ultra low-fat diet (with less than 20% of calories derived from fat) may be contraindicated in individuals who suffer both heart disease and depression. Although low-fat diets have demonstrated benefits for some people with heart disease, such diets tend to be seriously deficient in omega-3 fatty acids. Some authorities have proposed that low-fat diets may even contribute to depression because of their low omega-3 content. All too often, low-fat diets are high in carbohydrates. For the 47 million Americans estimated to have metabolic syndrome, a high-carbohydrate diet may magnify heart disease risk.32 It can also result in most fat intake coming from omega-6 fatty acids, compounds that increase thromboxane A2, a pro-inflammatory and vessel-constrictive agent that contributes to heart disease and may promote the depressive syndrome.

When fish oil is given to people suffering from depression, mood is substantially improved. A small, placebo-controlled trial conducted by Lauren Marangell, MD, chief of psychopharmacology at the Baylor College of Medicine, demonstrated improved mood in depressed persons following six weeks of treatment with 2 grams per day of DHA in a trial of 36 patients.33 A similar study at the Taiwan Medical University in China compared higher doses of fish oil (9.6 grams per day) with placebo in 28 patients with major depression. Substantial improvement in mood using a standardized rating assessment was experienced only in the group receiving fish oil.34 In another study, Andrew Stoll, MD, of Harvard examined 30 patients suffering from difficult-to-treat bipolar disorder (manic depression). Daily consumption of 6.2 grams of EPA and 3.4 grams of DHA resulted in objective improvement in depression scores and longer periods of remission between relapses.35

“For decades, researchers have been asking the chicken and the egg question: does depression cause heart disease or does heart disease cause depression? As with depression, heart disease is approximately 50 times more prevalent in nations with low levels of fish consumption compared to countries at the top of the fish-eating scale.”

—Andrew Stoll, MD
Harvard University
Perhaps the most persuasive clinical evidence documenting the mood benefits of omega-3s was seen in people who already take conventional antidepressant medication. An Israeli study of 20 patients with major depression who were receiving maintenance antidepressant pharmaceutical therapy showed that mood markedly improved after only three weeks of EPA supplementation when compared to placebo. Dr. Malcolm Peet, head of the Omega-3 Mental Health Research Group at the University of Sheffield (England), reported a study of 70 patients on conventional antidepressant therapy. In this trial, dramatic improvement in measures of depression was seen when 1 gram of EPA per day was added to the treatment regimen. Curiously, doses of 2 and 4 grams did not show statistically significant benefits.

Likewise, solid data demonstrate the benefits of omega-3 fatty acids in reducing risk for cardiovascular disease. The Italian GISSI Prevenzione Trial of more than 11,000 participants neatly showed that 850-882 mg of EPA and DHA resulted in a 30% reduction in death from cardiovascular disease and a 45% reduction in sudden cardiac death. These numbers equal or exceed the magnitude of benefits claimed by the cholesterol-reducing statin agents. The large number of participants in the GISSI study makes these observations virtually unassailable. Another study of 360 patients with symptoms of heart attack showed that patients given 1008 mg a day of EPA and 720 mg a day of DHA suffered 48% fewer cardiac deaths and 76% fewer sudden cardiac deaths, as well as a 54% reduction in dangerous heart rhythms.

Fish oil likely achieves these benefits through a broad spectrum of mechanisms, including increased cell membrane fluidity (affecting signal transduction), suppression of abnormal heart rhythm-generating activity, and marked reductions of triglycerides and the very low-density fraction of lipoproteins that can lead to the formation of dangerous "small" LDL particles and a drop in beneficial HDL. Fish oil also reduces the blood-clotting protein fibrinogen and inhibits platelet aggregation, both of which can prevent blood clot formation on active, ruptured coronary plaque that can contribute to a heart attack.

In the US, prevention of heart disease is an area of huge neglect. Treatment of major depression is likewise an imperfect practice, with less-than-optimal responses to antidepressant medication being an everyday phenomenon. Omega-3 fatty acids may indeed be a missing link that provides substantial benefits in both areas with virtually no downside. While the concomitant treatment of heart disease and depression with fish oil has never been formally examined in a clinical trial, it remains a compelling topic worthy of further examination.

Fish oil is the most concentrated source of the omega-3 fatty acids EPA and DHA. A secondary source is alpha-linolenic acid (ALA), which is found in flaxseed, walnuts, and canola oil. However, only 10% of ALA ingested from food is converted into active EPA or DHA; much of it is simply burned for calories. Fish oil thus remains the most potent source of omega-3 fatty acids.

**Benefits of Folic Acid and SAMe**

Depressed, hostile, or angry people have higher homocysteine levels. If homocysteine leads to coronary plaque growth and heart attack, will folic acid and B vitamins that
lower homocysteine improve mood and reduce heart attack?

The data strongly suggest that folic acid supplementation elevates mood, both in people already taking antidepressant medication and in those who are not. Indeed, five clinical trials, though all relatively small (each with fewer than 100 patients), have consistently demonstrated improvements in depression measures when patients are given various doses of folic acid. For instance, in a 1993 study of 96 patients at the University of Parma, Italy, folic acid supplementation yielded improvements in mood similar to those of conventional antidepressants. Another study by Drs. Alec Coppen and John Bailey in Surrey, England, showed that response to prescription fluoxetine (Prozac) was substantially improved by taking as little as 500 mcg of folic acid a day.

Though few psychiatrists have added folic acid to their arsenal of antidepressant therapeutics, the data suggest that this simple, inexpensive treatment should be a part of every depressed person's panel of therapies. Doses of only 1-5 mg would be required, generally along with 25-50 mg of vitamin B6. Vitamin B12 should always be taken with folic acid to help guard against a hidden B12 deficiency.

The growing experience with folic acid treatment in people at risk for cardiovascular disease includes three clinical trials suggesting that folic acid reduces the growth of plaque in the carotid arteries (a surrogate for coronary plaque growth) and reduces the likelihood of future heart attack. The Canadian group at the Stroke Prevention and Atherosclerosis Research Centre in Ontario reported an investigation in 101 patients showing that a homocysteine level greater than 14 mmol/L identified a group that showed much more rapid growth of carotid plaque. Daily treatment with 2.5 mg of folic acid, 25 mg of vitamin B6, and 250 mcg of vitamin B12 eliminated plaque growth. The Dutch group at Vrije Universiteit in Amsterdam has reported extensively on treating high homocysteine levels using folic acid and vitamin B6 in patients with peripheral arterial disease (usually of the leg arteries), demonstrating reduction of heart attack, slowed growth of carotid and leg artery plaque, and diminished likelihood of death.

Folic acid supplementation increases levels of the homocysteine metabolite s-adenosyl-L-methionine, or SAMe. Some have speculated that the mood-elevating properties of folic acid may be at least partly due to an increase in endogenous SAMe, since SAMe has been shown in numerous studies to be an effective antidepressant supplement. Since 1973, over 40 clinical trials have demonstrated the effectiveness of SAMe in elevating mood in the depressed, including a total of 537 patients in 13 randomized, double-blind studies. In 18 trials pitting SAMe head to head against the conventional antidepressants imipramine, chlorimipramine, and others, SAMe proved equally effective, and it is essentially without side effects.

SAMe has been available in the US as an over-the-counter supplement since 1997, though it has been available over the counter or by prescription in Europe for over 20 years. SAMe at a dose of 400 mg per day yields blood levels in the range believed to induce antidepressant benefits, though some clinicians have noted that doses up to 1600 mg daily are required for some individuals. It is interesting to speculate that the combination of folic acid and SAMe might yield even greater benefits and more powerfully improve mood and many of the downstream phenomena leading to coronary disease risk. This remains an area for further research.

Folic acid supplementation, therefore, likely improves mood while lowering homocysteine and thus the risk of heart attack. Along with fish oil and omega-3 fatty acids, folic acid represents another intriguing "missing link" between two disparate diseases with an exciting potential for common treatments.
"[Metabolic syndrome] is considered a 'multiplex' cardiovascular risk factor, in that each component of the cluster of abnormalities is a risk factor in its own right."
—Scott Grundy, MD, PhD
University of Texas Southwestern

Depression and Metabolic Syndrome

As the US population gets heavier and heavier, metabolic syndrome becomes increasingly more prevalent. One in every four American adults suffers from this common condition, which represents a combination of lifestyle and genetic factors. Because depressed people are more likely to develop metabolic syndrome, this disorder is another important mediator of the interplay between mood and heart disease.

Most of us have seen someone who, when struck with depression or impaired by other chronic negative emotions, burrows into a lifestyle of physical inactivity and overeating. The resulting weight gain activates all the latent characteristics of the tragically common metabolic syndrome (increased abdominal fat, hypertension, low HDL, resistance to insulin—dubbed “the deadly quartet” by Dr. Norman Kaplan in 1989). This familiar sequence can greatly magnify risk for heart disease.

But can the reverse occur? Can a person become overweight through neglect or indulgence, develop metabolic syndrome, then trigger depression and the cascade of events leading to heart disease? If this flip-flop in the sequence of events were true, then efforts aiming squarely at managing weight and metabolic syndrome should be among our principal health concerns.

A fascinating study conducted by Drs. Katri Raikkonen of the University of Helsinki (Finland) and Lewis Kuller of the University of Pittsburgh attempted to untangle this question. Psychological and metabolic measures were obtained in 425 middle-aged females. Seven and a half years later, these same measures were repeated. Raikkonen and Kuller reported that women with emotional characteristics of anger, depression, and anxiety at initial enrollment were more likely to develop metabolic syndrome. Even more interestingly, women without these psychological traits but with metabolic syndrome at the start were more likely to develop anger, anxiety, and depression by the end of the study. In other words, in this second group, abdominal fat, high blood pressure, low HDL, and insulin resistance—all the features of metabolic syndrome—predicted a future of negative emotions. By either route, the result is a person with the physiological stage set for development of heart disease.

How to Lose Weight Faster

Metabolic syndrome is, in the great majority of cases, a disease of the overweight and obese. If metabolic syndrome leads to depression and other negative emotions that further escalate the risk of heart disease, that is all the more reason to attack metabolic syndrome. Not surprisingly, the most direct, effective way to do so is to lose weight. Weight loss might then be a useful path to reducing the risk of both depression and heart disease. Unfortunately, that is easier said than done.

Carbohydrate-restricted programs, popularized by the Atkins and South Beach diets, are helpful weight-loss tools, though the high-saturated-fat, low-fiber approach of the Atkins’ “induction phase” makes it unhealthy for a period any longer than several weeks. In the author’s experience, people with metabolic syndrome respond in an exaggerated manner to these diets, losing weight rapidly. Losses of 10-20 pounds in the first month are not uncommon.

Along with diet, several nutritional supplements can supercharge weight-loss efforts and thereby improve many features of metabolic syndrome. They include:

**White bean extract.** This supplement blocks intestinal carbohydrate absorption by 66%. Taking 1500 mg twice a day with meals can lead to 3-7 pounds of weight loss in the first month of use. Like its prescription counterpart (acarbose), it can cause excess gas, though usually modest. Do not succumb to the temptation to indulge in carbohydrates, since the blocking effect is only partial. You can overcome the effect quite easily, for instance, with a 50-gram carbohydrate load of just two granola bars.
Calcium pyruvate. Doses of 2500 mg twice a day act as a weight-loss accelerator that is safe and ephedra-free. Calcium pyruvate also has the interesting property of "exercise enhancement," making exercise easier and less taxing, and encouraging exercise that is longer and harder with a smoother recovery.  

Chromium. This trace mineral provides an insulin-sensitizing benefit along with a modest effect of promoting weight loss (see "Chromium: An Element Essential to Health," Life Extension, August 2004). The dose ranges from 600 to 1000 mcg per day and is best used consistently over a period of several months. Work with your doctor to monitor your blood sugar if you have established diabetes or take medication to lower your blood sugar before you begin taking chromium.

Testosterone. Contrary to popular belief, testosterone supplementation in men is more useful in improving mood than in stoking libido. Feelings of sadness, fatigue, anger, and even severe depression may be associated with declining blood levels of testosterone in men in their forties and beyond. Testosterone can often result in dramatic improvement in these symptoms (see "A New, Independent Risk Factor for Heart Disease," Life Extension, August 2004). Testosterone not only improves the psychological side of the equation, but also can improve many characteristics of metabolic syndrome through its weight-loss-promoting effects.  

Carnitine is a supplement that may be equal to testosterone in its ability to improve sexual function, boost low moods, increase energy, and promote weight loss through its effect on fat and glucose metabolism. A dose of 2000 mg per day of acetyl-L-carnitine has been found effective in most studies.  

DHEA is an adrenal hormone whose beneficial effects include its considerable ability to elevate mood, particularly in men and women with lower blood levels of DHEA-sulfate. Among the most persuasive reports is a 1999 study conducted at the National Institute of Mental Health in which 90 mg per day of DHEA significantly improved symptoms such as anhedonia (loss of interest), loss of energy, lack of motivation, emotional "numbness," sadness, inability to cope, and worry in men and women aged 45-63. DHEA also improves some features of metabolic syndrome by increasing sensitivity to insulin, decreasing constriction of the body's arteries (endothelial function), and reducing plasminogen activator inhibitor-1, a potent blood-clot-promoting protein. The most common dose is 25 mg for women aged 45 and older, and 25-50 mg for men aged 40 and older.

PGX™ is a highly viscous fiber blend of glucomannan, xanthan, and alginate that limits sugar absorption and the subsequent after-meal insulin spike. This sugar-limiting effect can occur when taking a relatively low dose of 1-3 grams before each meal. A related benefit is a modest reduction in total cholesterol and LDL. (See "Novel Fiber Limits Sugar Absorption," Life Extension, September 2004.)

Exercise is another therapeutic tool that simultaneously addresses both metabolic syndrome and risk factors and psychological well-being. Regular exercise can help improve mood, reduce symptoms of depression and anxiety, and promote overall health and longevity.
for heart disease. Exercise is an effective strategy to lose weight, improve insulin sensitivity, and lower levels of stress hormones. Aerobic exercise has the added capacity to improve mood. In fact, 16 weeks of exercise can be as effective as prescription antidepressant medication for depression.  

**Conclusion**

Depression and other negative emotions interact with coronary heart disease risk through a complex web of metabolic pathways. The clinical data are quite clear: depression, anxiety, anger, and other chronic, negative emotions substantially increase the risk of heart disease. They also contribute to development of metabolic syndrome, a potent risk factor for heart disease and diabetes.

Several nutritional supplements can be powerful additions to a program for improving mood and preventing heart disease. Fish oil stands out as the "missing link," with research demonstrating impressive evidence of its benefits in both improving mood and reducing the risk of heart disease. Homocysteine is another potential link. Data suggest that the use of B vitamins, particularly folic acid, to reduce homocysteine translates into impressive improvement in mood and reduction of cardiovascular events.

Metabolic syndrome is now rampant across the US. This constellation of physiological disruptions triggered by weight gain can generate negative emotions as well as increased risk of heart disease. Weight loss is the most direct way to address metabolic syndrome and thereby reduce or eliminate its ill effects on health. 

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