

Omega-3 Fatty Acids, Homocysteine, and the Increased Risk of Cardiovascular Mortality in Major Depressive Disorder

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Depression is associated with elevated rates of cardiovascular morbidity and mortality. This elevation seems to be due to a significantly increased risk of coronary artery disease and myocardial infarction and, once the ischemic heart disease is established, sudden cardiac death. Recent data suggest that the increased rates of cardiovascular disease in patients with depression may be the result of one or more still-unrecognized underlying physiological factors that predispose a patient to both depression and cardiovascular disease. Two possibly related factors that may have a causal relation with both depressive disorders and cardiovascular disease are an omega-3 fatty acid deficiency and elevated homocysteine levels. We present the available data connecting cardiovascular disease, depression, omega-3 fatty acids, and homocysteine. In addition, we suggest research strategies and some preliminary treatment recommendations that may reduce the increased risk of cardiovascular mortality in patients with major depressive disorder. (HARVARD REV PSYCHIATRY 2001;9:280-293.)

Depression (major depressive disorder as well as depressive symptoms) is associated with higher rates of cardiovascular morbidity and mortality.¹ The elevated rates seem to be due to a significantly increased risk of developing coronary ar-

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tery disease and myocardial infarction²⁻⁴ and, once the ischemic heart disease is established, suffering a fatal cardiac event.⁵⁻⁸ Severe ventricular arrhythmias resulting in sudden cardiac death appear to be the leading cause of mortality in patients with depression and coronary artery disease.^{6,9-14} Furthermore, depression appears to be associated with an increased risk of developing cerebrovascular disease.^{15,16}

The pathophysiology underlying the association between cardiovascular disease and depression remains unclear. Components of "syndrome X" have been shown to be present in a significantly higher percentage in patients suffering from a major depressive episode than in controls.¹⁷ The term "syndrome X" was first introduced in 1988¹⁸ to describe a cluster of risk factors for coronary artery disease (i.e., glucose intolerance, hyperinsulinemia, increased very-low-density lipoprotein triglyceride, and decreased high-density lipoprotein cholesterol) occurring in individuals with high blood pressure, with insulin resistance being the common feature and basic abnormality. Newer antidepressants such as fluoxetine have been shown to improve glycemic control in patients with¹⁹ and without²⁰ major depression, while older tricyclics such as nortriptyline failed to do so in patients with major depression.²¹ Whether antidepressants are able to reverse visceral obesity,²² another component of "syndrome

X,²³ in patients with a major depressive episode is less certain.²⁴ At present, even though serotonergic antidepressants such as sertraline appear safe and effective in treating the mood symptoms of a major depressive episode following myocardial infarction, it remains unknown whether such agents can diminish the potentially fatal impact of major depressive disorder on cardiovascular mortality.²⁵ Whether psychosocial interventions can beneficially influence the increased risk of cardiovascular mortality in depression is also unknown.^{26,27}

Two recent studies,^{3,28} however, have cast doubt on the concept that the aforementioned metabolic risk factors for heart disease and/or stroke associated with a major depressive episode are solely responsible for the increased risk of cardiovascular mortality in patients with major depressive disorder. A recent 13-year prospective cohort study³ showed that the odds of myocardial infarction in persons with a history of dysphoria (who never met the criteria for major depressive disorder) are 2.1 times as high as those seen in persons with no history of 2 weeks of dysphoria. And in a study of patients who initially sought treatment for major depressive disorder, mania, or schizoaffective disorder,²⁸ chronicity of depressive symptoms during follow-up did not predict cardiovascular death. These results suggest that the increased rates of cardiovascular disease in patients with depression may be the result of a still-unrecognized underlying physiological factor or factors that predispose a person to both depression and cardiovascular disease.

OMEGA-3 FATTY ACIDS, HOMOCYSTEINE, AND CARDIOVASCULAR DISEASE: AN OVERVIEW

Two possibly related factors that may have a causal relation with both depressive disorders and cardiovascular disease are an omega-3 fatty acid deficiency and elevated homocysteine levels. Omega-3 fatty acids are a group of essential polyunsaturated lipids. Dietary sources of omega-3 fatty acids include flaxseeds and flaxseed oil (α -linolenic acid [ALA]) and fatty fish and fish oils (eicosapentaenoic acid [EPA], docosahexaenoic acid [DHA]). Low concentrations of omega-3 fatty acids in red blood cells are associated with increased risk of sudden cardiac death²⁹ and have also been reported in patients with major depressive disorder.^{30–32} Homocysteine is a sulfur-containing nonessential amino acid metabolized by two different chemical reactions: remethylation and transsulfuration. In the remethylation pathway, homocysteine is remethylated to methionine, which requires *N*-5-methyltetrahydrofolate (a folic acid derivative) and vitamin B₁₂ (a cofactor for methionine synthase), with subsequent activation of methionine by adenosine triphosphate to form *S*-adenosylmethionine (SAM). For the transsulfuration reaction, homocysteine is converted to cystathionine by cystathionine beta-synthetase—which requires vitamin

B₆ (pyridoxal-5'-phosphate) as a cofactor.^{33,34} Elevated plasma homocysteine levels are associated with an increased risk of atherosclerosis³⁵ and have also been reported in patients with major depressive disorder.^{36–38} Furthermore, neither omega-3 fatty acid deficiency nor elevated homocysteine seems to respond favorably to mood-elevating treatment with conventional antidepressant drugs in patients with major depressive disorder.^{37,39}

We will review the available data connecting cardiovascular disease, depression, omega-3 fatty acids, and homocysteine. In addition, we will suggest research strategies and priorities to advance the understanding of this emerging field. Finally, we will provide some preliminary treatment recommendations, based on the available data, that may reduce the increased risk of cardiovascular mortality in patients with major depressive disorder.

METHODS

We performed a *Medline* search using the following keyword combinations: “depressive disorder” or “depression” and “cardiovascular diseases”; “depressive disorder” or “depression” and “omega-3 fatty acids”; “depressive disorder” or “depression” and “homocysteine”; “omega-3 fatty acids” and “homocysteine”; “cardiovascular diseases” and “homocysteine” and “clinical trial”; “myocardial infarction” and “omega-3 fatty acids” and “clinical trial.” Additional relevant literature was found by searching the reference lists of the retrieved articles. The literature search was limited to articles published in English or German from 1986 through 2000.

OMEGA-3 FATTY ACIDS AND CARDIOVASCULAR DISEASE

The most recent dietary guidelines from the American Heart Association⁴⁰ recommend the consumption of at least two servings of fatty fish per week for the general population to reduce the risk of cardiovascular disease.⁴⁰ The strongest evidence for the protective effects of omega-3 fatty acids in cardiovascular disease comes from four controlled, randomized secondary prevention trials in which they were added to standard medication treatment, such as beta-blockers, calcium-channel blockers, antiplatelet agents, anticoagulant agents, and angiotensin-converting enzyme inhibitors, in patients who had suffered a myocardial infarction^{41–45} (see Table 1 for a summary of these studies). Probably due to the antiarrhythmic properties of omega-3 fatty acids,^{41,46,47} these trials consistently showed a reduction in overall mortality, largely because of a reduction in cardiac deaths, and sudden cardiac death in particular. The results for nonfatal cardiovascular events are controversial, with no advantages seen with fish⁴² or fish oil⁴⁵ but beneficial effects reported for ALA.^{43,44} However, other aspects of the Mediterranean diet,

TABLE 1. Studies of Omega-3 Fatty Acids for the Secondary Prevention of Myocardial Infarction

Study	Subjects	Study design/methods	Results
Burr et al. ⁴²	2033 M less than 70 y old hospitalized for acute MI	2-y randomized, controlled clinical trial. All subjects randomly allocated to receive or not receive advice on each of three dietary factors: reduction in fat intake and increase of PUFAs (n = 1018), increase in fatty fish intake (n = 1015), and increase in cereal fiber intake (n = 1017).	At 2 y, the fish-advice group showed, compared with the other groups combined, a 29% reduction in all-cause mortality (ARR, 0.71; CI, 0.54–0.93; <i>p</i> < 0.05)—a difference entirely attributable to a reduction in IHD deaths—and a 16% reduction in all IHD events (ARR, 0.84; CI, 0.66–1.07; NS). More nonfatal MIs occurred in the fish-advice group than in the other groups (4.8% vs. 3.2%; NS). Weekly intake of EPA in the fish-advice group was 2.5 g (about 300 g of fatty fish).
De Lorgeril et al. ^{43,44}	605 patients (M/F) less than 70 y old with an MI during previous 6 mo	5-y randomized, controlled, single-blind trial. Experimental group (n = 302) ate a Mediterranean diet rich in ALA (estimated ALA intake, ca. 2 g/d); control group (n = 303) ate a prudent Western-type diet (estimated ALA intake, ca. 0.6 g/d).	At follow-up (mean, 46 mo), the experimental group had, compared to the control group, a 56% reduction in all-cause deaths (ARR, 0.44; CI, 0.21–0.94; <i>p</i> = 0.03), a 65% reduction in cardiac deaths (ARR, 0.35; CI, 0.15–0.83; <i>p</i> = 0.01), and a 72% reduction in cardiac deaths/nonfatal MIs (ARR, 0.28; CI, 0.15–0.53; <i>p</i> = 0.0001). ALA was the only fatty acid significantly associated with improved prognosis (ARR, 0.20; CI, 0.05–0.84). No strokes occurred in the experimental group, whereas 4 occurred in the control group. At a mean follow-up of 27 mo, there were 8 sudden deaths in the control group and 0 in the experimental group.
Singh et al. ⁴¹	360 patients (M/F) with suspected acute MI (onset of symptoms in the preceding 24 h)	1-y randomized, double-blind, placebo-controlled trial. Fish-oil group (n = 122) received 1.08 g/d of EPA and 0.72 g/d of DHA; mustard-oil group (n = 120) received 20 g/d of mustard oil (2.9 g/d of ALA); placebo group (n = 118) received 1mg/d of aluminum hydroxide.	At 1 y, the fish-oil group and the mustard-oil group had, compared with the placebo group, a 48% reduction (RR, 0.52; CI, 0.22–1.21; <i>p</i> < 0.01) and a 40% reduction (RR, 0.60; CI, 0.23–1.40; <i>p</i> < 0.01), respectively, in total cardiac deaths, a 54% reduction (RR, 0.46; CI, 0.21–0.98; <i>p</i> < 0.05) in total arrhythmias, and a 76% reduction in sudden cardiac deaths (1.6% in both the fish-oil group and the mustard-oil group vs. 6.6% in the placebo group; RR, 0.24; CI, 0.03–2.0; NS).
Anonymous ⁴⁵	11,324 patients (M/F), any age, with an MI during previous 3 mo	3.5-y randomized, controlled clinical trial. Omega-3 fatty acids group (n = 2836) received 850–882 mg/d EPA and DHA (average EPA:DHA ratio = 1:2); vitamin E group (n = 2830) received 300 mg of vitamin E daily; omega-3 fatty acids + vitamin E group (n = 2830) received both; control group (n = 2828) received no supplement.	At 3.5 y, the omega-3 fatty acids group had, compared with the control group (4-way analysis), a 20% reduction in total deaths (RR, 0.8; CI, 0.67–0.94; <i>p</i> -value not provided), a 30% reduction in cardiovascular deaths (RR, 0.7; CI, 0.56–0.87; <i>p</i> = 0.024), and a 45% reduction in sudden cardiac deaths (RR, 0.55; CI, 0.4–0.76; <i>p</i> = 0.01). No significant reduction was reported in nonfatal cardiovascular events in the omega-3 fatty acids group (RR, 0.96; CI, 0.76–1.21). There was a 30% increase in fatal and nonfatal stroke (1.9% vs. 1.5%; RR, 1.30; CI, 0.87–1.96; NS) in the omega-3 fatty acids group compared with the control group.

AHA, American Heart Association; ALA, α -linolenic acid; ARR, adjusted risk ratio; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; F, female; IHD, ischemic heart disease; M, male; MI, myocardial infarction; NS, not significant; PUFAs, polyunsaturated fatty acids; RR, risk ratio.

such as a lower cholesterol intake and a higher intake of fruits, might also account for this finding.^{43,44}

OMEGA-3 FATTY ACIDS AND AFFECTIVE DISORDERS

Several distinct yet convergent lines of evidence point to a possible involvement of particular omega-3 fatty acids in mood disorders. Although earlier studies^{48,49} measuring omega-3 fatty acids in plasma phospholipids of patients with depression yielded somewhat contradictory results, recent investigations examining omega-3 fatty acid levels in red blood cell membranes^{30–32} yielded more-consistent findings (see Table 2 for a summary of these studies). Polyunsaturated fatty acid levels in red blood cells are a better indication of functionally available omega-3 and omega-6 fatty acids than are plasma phospholipid profiles.^{50,51}

The studies show a significant reduction of total omega-3 fatty acids,^{31,32} as well as single omega-3 fatty acids such as EPA³¹ and DHA,³² in the red blood cell membranes of patients with major depressive disorder compared with healthy controls. Furthermore, saturated fatty acids such as palmitic and stearic acids, and monounsaturated fatty acids such as oleic acid, seem to be increased in patients with major depression compared to controls.³² The results for omega-6 fatty acids are less consistent across the studies: one investigation³¹ reported no difference,³¹ whereas another³² found a smaller-sized reduction in these fatty acids than in omega-3 fatty acids. Since the incubation of red blood cells from controls with hydrogen peroxide abolished all significant differences between patients and control subjects, *in vivo* lipid peroxidation in the depressed group might be at least partially responsible for the differences in the lipid composition of red blood cells.³² Lipid peroxidation is believed to play a fundamental role in the pathogenesis of atherosclerotic vascular disease.⁵³ A recent study⁵⁴ has shown similar significantly increased levels of lipid peroxidation in antidepressant-treated patients with major depressive disorder ($p < 0.001$) and patients with coronary artery disease ($p < 0.001$) compared with healthy controls.

One study³⁹ also shows that in depressed patients, dietary intake of ALA and levels of ALA in red blood cell membranes are strong predictors of the severity of depression and are negatively correlated with scores on the Beck Depression Inventory. These findings for ALA are consistent with the results of an open-label study⁵⁵ in which dietary flaxseed oil (a daily dose of 0.1–0.5 g of ALA per kg of body weight, or 2–6 tablespoons) showed potent antidepressive properties in two out of three lithium-responsive patients with unipolar depression.

Finally, the studies^{31,32} also suggest that antidepressant treatment does not seem to influence/reverse the polyunsaturated fatty acid abnormalities in red blood cell membranes.

Although the regular (nonsupplemented) dietary intake of EPA in depressed subjects was not found to correlate negatively with severity of depression,^{30,31} high-dose EPA/DHA (fish oil) supplementation has recently been shown to have mood-stabilizing and antidepressive properties in patients with unstable bipolar disorder.⁵⁰ This finding is in accord with epidemiological data^{56,57} indicating that nations with high fish consumption have significantly lower rates of major depression ($r = -0.84$, $p < 0.005$). Additional uncontrolled data⁵⁸ suggest that changing from a traditional high-salmon diet to a low-EPA modern diet is associated with increased prevalence of major depression among coastal Native Americans in British Columbia. Interestingly, reintroducing traditional foods was reported to have improved the mental health in this community.

A substantial number of patients with affective disorders may therefore suffer from a functional omega-3 deficiency syndrome resulting from either an insufficient dietary intake and/or a disturbed omega-3 fatty acid metabolism, such as enhanced omega-3 fatty acid peroxidation. Preliminary data^{31,50,55} indicate that ALA and fish oil might have antidepressant properties in affective disorders. However, successful serotonergic antidepressant treatment does not lead to a normalization of the altered fatty acid profile.³⁹

HOMOCYSTEINE AND CARDIOVASCULAR DISEASE

Plasma homocysteine levels above 9–10 $\mu\text{mol/L}$ represent a graded independent risk factor for arteriosclerotic vascular diseases. A 5- $\mu\text{mol/L}$ increment in total plasma homocysteine is believed to elevate the risk of coronary artery disease by as much as would a cholesterol increase of 0.5 mmol/L (20 mg/dL).^{35,59,60} Furthermore, preliminary data⁶¹ also indicate that elevated plasma homocysteine levels on admission to the hospital might also predict subsequent cardiac events, including sudden cardiac death, in patients with acute coronary syndromes.

Over the past 2 years, three controlled clinical trials have been published examining the effects of vitamin supplementation on atherosclerosis^{62–65} (see Table 3 for a summary of these studies). These investigations indicate that vitamin supplementation might decrease carotid plaque in patients with unexplained rapid progression of atherosclerosis and homocysteine levels either above or below 14 $\mu\text{mol/L}$. Furthermore, they suggest that treatment with folic acid and vitamin B₆ abrogates the hyperhomocysteinemia-associated increased risk of cardiovascular events in patients with premature peripheral arterial occlusive disease.⁶⁴ Finally, lowering homocysteine seems to slow the progression of subclinical cardiac atherosclerosis among healthy siblings of patients with premature atherothrombotic disease.⁶⁵ This beneficial effect was independent of the total plasma

TABLE 2. Studies of Omega-3 Fatty Acids and Affective Disorders

Study	Subjects	Study design/methods	Results
Adams et al. ³⁰	20 in- and outpatients with DSM-IV unipolar depression (all but 3 drug-free), HAM-D scores 14.5–36	Clinical study. Dietary intake of lipids over the previous 3 mo assessed with the Food Frequency Questionnaire; RBC phospholipid and plasma PUFA levels measured; severity of depression determined with the 21-item HAM-D and a linear rating scale.	RBC phospholipid AA:EPA ratio was positively correlated with the severity of depression, measured with the HAM-D ($r = 0.472, p < 0.05$) and the linear rating scale ($r = 0.729, p < 0.01$); RBC phospholipid EPA level was negatively correlated with the severity of depression, measured with the linear rating scale ($r = -0.546, p < 0.05$). No significant correlations were found between estimated EPA intake from fish and either RBC EPA level or RBC AA:EPA ratio.
Edwards et al. ³¹	10 patients with a DSM-IV major depressive episode, all taking antidepressant medication, and 14 healthy age- and gender-matched controls	Controlled clinical study. All subjects assessed with the BDI; current diet assessed with the 7-d weighed intake method; RBC membrane omega-3 fatty acids, omega-6 fatty acids, and saturated and monounsaturated fatty acids measured.	Patients showed a significant decrease in RBC membrane n-3 PUFA levels (EPA, $p = 0.02$; DHA, $p = 0.02$; total n-3, $p = 0.02$) compared to controls but no significant abnormalities in n-6 PUFAs. Smoking and recent stressful life events had no significant effect on RBC membrane levels of individual or total n-3 fatty acids. Patients and controls did not differ significantly in current dietary intake of n-3 fatty acids or total energy intake. Among the depressed patients, dietary ALA ($r = -0.83, p = 0.003$) and RBC membrane ALA ($r = -0.81, p = 0.008$) were the only strong predictors of BDI scores.
Peet et al. ³²	15 patients with a DSM-IV major depressive episode (unipolar illness), free of psychotropic medication for at least 7 d (mean, 16.7 ± 20 days), and 15 healthy age- and gender-matched controls	Controlled clinical study. Comparison of RBC membrane fatty acid levels in patients and controls. A second blood sample was drawn from 10 of the patients after 6 wk of antidepressant treatment with lofepramine or amisulpiride.	Patients showed a significant depletion in RBC membrane fatty acid levels of DHA ($p = 0.009$), DPA ($p = 0.04$), total n-3 ($p = 0.02$), linoleic acid ($p = 0.005$), DGLA ($p = 0.02$), and total n-6 ($p = 0.02$) compared with controls. Patients also had nonsignificantly elevated AA:EPA and AA:DHA ratios ($p = 0.2$ and 0.06 , respectively) and significantly elevated levels of oleic acid ($p = 0.001$), palmitic acid ($p = 0.03$), and stearic acid ($p = 0.02$) compared with controls. Patients, both before and after treatment, had lower DHA ($F = 4.0, p = 0.03$) and total RBC n-3 ($F = 3.61, p = 0.04$) levels than did controls; the difference disappeared after incubation of RBCs with hydrogen peroxide in controls.
Stoll et al. ⁵⁰	30 patients with unstable DSM-IV bipolar disorder (type I or II), 8 of whom had no preexisting medication	4-mo randomized, double-blind, placebo-controlled trial. In addition to any preexisting medication, patients in the experimental group received 6.2 g EPA and 3.4 g DHA daily, and those in the control group received 9.6 g olive oil daily.	The experimental group had a longer period of remission than did the control group ($p = 0.002$; Mantel-Cox). This applied to the 8 patients with no preexisting medication, as well (none of the 4 randomly assigned to omega-3 fatty acids suffered from a relapse, whereas 3 of the 4 on placebo relapsed [$p = 0.04$; Mantel-Cox]). The experimental group also performed better than did controls on the HAM-D ($z = -3.14, p = 0.002$) but not on the YMRS (z -value not supplied, $p = 0.21$).

AA, arachidonic acid; ALA, α -linolenic acid; BDI, Beck Depression Inventory; DGLA, dihomogammalinolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EPA, eicosapentaenoic acid; HAM-D, Hamilton Rating Scale for Depression; PUFA, polyunsaturated fatty acid; RBC, red blood cell; YMRS, Young Mania Rating Scale.

TABLE 3. Studies of the Effects of Homocysteine-Lowering Vitamin Supplementation on Atherosclerosis

Study	Subjects	Study design/methods	Results
De Jong et al. ⁶⁴	232 patients with clinically manifest peripheral arterial occlusive disease with onset before age 56 y; 70 (30%) had hyperhomocysteinemia after methionine loading (Group A), while 162 (70%) had normal postmethionine levels (Group B)	Controlled clinical trial with mean follow-up of 20 mo. Experimental group (Group A) received 250 µg of vitamin B ₆ plus 5 mg of folic acid daily; control group received no homocysteine-lowering treatment.	During the follow-up period, 29.6% of Group A patients and 32.9% of Group B patients had a new cardiovascular event (ARR [Group A vs. Group B], 0.76; CI, 0.33–1.74). In Group B alone, higher plasma homocysteine levels were associated with an increased risk of new cardiovascular events (RR per 1 µmol/L of fasting homocysteine levels, 1.17; CI, 1.05–1.30).
Hackam et al., ⁶³ Peterson & Spence ⁶²	101 patients with unexplained rapid progression of atherosclerosis; 51 had plasma homocysteine levels > 14 µmol/L (Group A) and 50 had levels ≤ 14 µmol/L (Group B)	Controlled clinical trial of vitamin therapy (add-on regimen: 2.5 mg of folic acid + 25 mg of pyridoxine + 250 µg of vitamin B ₁₂ daily). The rate of progression of carotid plaque was determined by 2-dimensional ultrasound of carotid arteries before and after the vitamin therapy.	Group A (mean duration of treatment before vitamin therapy, 2.6 y ± 1.4 y; vitamin therapy, 1.8 ± 0.7 y): plaque area progressed by 0.21 ± 0.41 cm ² /y before vitamin therapy and by -0.049 ± 0.24 cm ² /y during vitamin therapy (<i>p</i> = 0.0001). Group B (mean duration of treatment before vitamin therapy, 2.7 ± 1.7 y; vitamin therapy, 1.6 ± 0.9 y): plaque area progressed by 0.13 ± 0.24 cm ² /y before vitamin therapy, and by -0.024 ± 0.29 cm ² /y during vitamin therapy (<i>p</i> = 0.022).
Vermeulen et al. ⁶⁵	158 healthy siblings of 167 patients with premature atherothrombotic disease and postmethionine hyperhomocysteinemia	2-y randomized, double-blind, placebo-controlled trial. Experimental group (n = 78) received 5 mg folic acid and 250 mg vitamin B ₆ daily, control group (n = 80) received placebo.	At 20 mo, the experimental group had, compared to the placebo group, a significant reduction in fasting (7.4 µmol/L vs. 12.0 µmol/L, <i>p</i> < 0.001) and postmethionine (34.9 µmol/L vs. 50.3 µmol/L, <i>p</i> < 0.001) plasma homocysteine concentrations. At 2 y, the experimental group showed, compared to the placebo group, a 60% reduction in the odds of having an abnormal exercise electrocardiography test (OR, 0.40; CI, 0.17–0.93; <i>p</i> = 0.035) (a result unaffected by adjustment for age, sex, and baseline concentration of postmethionine total homocysteine [OR, 0.38; CI, 0.16–0.91; <i>p</i> = 0.03]), but no decreased rate of peripheral arterial abnormalities (ankle brachial index: OR, 0.87; CI, 0.56–1.33; <i>p</i> = 0.51; duplex scanning of femoral artery: OR, 1.02; CI, 0.26–4.05; <i>p</i> = 0.98; duplex scanning of carotid artery: OR, 0.86; CI, 0.47–1.59; <i>p</i> = 0.75).

ARR, adjusted relative risk; CI, confidence interval; OR, odds ratio; RR, relative risk.

homocysteine concentration after methionine loading. The methionine-load test measures homocysteine before and after the intake of 100 mg of methionine per kilogram of body weight. It may help to identify persons who have homocysteine-related cardiovascular disease risk despite normal fasting homocysteine values.⁶⁶

These preliminary results suggest that lowering homocysteine levels with vitamin supplementation (folic acid, vitamin B₆, and vitamin B₁₂) favorably affects the evolution of arterial occlusive diseases in persons who are affected by or at risk for atherosclerotic vascular disease. However, folic acid and vitamin B₆ might also exert their beneficial effect

on the progression of atherosclerosis by properties independent of their effect on homocysteine concentrations.^{67–69}

HOMOCYSTEINE AND AFFECTIVE DISORDERS

Mean homocysteine levels have been shown to be higher in patients with major depressive disorder than in healthy or neurological controls.³⁶ (See Table 4 for a summary of studies on homocysteine and affective disorders.) In one investigation³⁸ 20% of depressed outpatients had homocysteine levels more than two standard deviations above the comparison mean of healthy adult volunteers ($>13.2 \mu\text{mol/L}$, versus $7.3 \mu\text{mol/L}$), whereas in the other³⁶ more than 50% of the depressed inpatients had a total plasma homocysteine concentration above the range seen in normal and neurological controls ($>12 \mu\text{mol/L}$, versus $3.4\text{--}11.9 \mu\text{mol/L}$). Given that studies^{70–73} suggest that homocysteine levels of $10 \mu\text{mol/L}$ or higher are associated with an increased risk of cardiovascular mortality, approximately 20–50% of patients with major depressive disorder may be at increased risk of cardiovascular mortality based on high serum homocysteine concentrations. Homocysteine levels were not related to either gender or age.³⁸ Baseline homocysteine concentration was not associated with subtype of major depressive disorder,³⁸ but patients with high homocysteine concentrations had higher Hamilton scores than did those with normal homocysteine levels.³⁶ Furthermore, homocysteine levels did not predict response to fluoxetine,³⁸ nor were they changed by treatment with fluoxetine.³⁷ However, lowering homocysteine levels in these patients with folic acid resulted in antidepressive actions superior to those seen in patients treated with fluoxetine alone.³⁷ At 10 weeks, total plasma homocysteine concentration was significantly positively correlated with Hamilton score in the fluoxetine plus folic acid treatment group, but not in the fluoxetine plus placebo group. Improvement was not related to plasma folate.³⁷ These antidepressant effects were limited to female patients, however. Male patients showed no significant change in plasma homocysteine in response to $500 \mu\text{g}$ folic acid daily in this study, which may be related to the observation that for any given dose of folic acid, men tend to show a smaller increase in folic acid and a smaller decrease in homocysteine than do women.⁷⁴ Therefore, $500 \mu\text{g}$ of folic acid may have been insufficient to produce a clear homocysteine-lowering effect in the male patients. The antidepressant effect of lowering homocysteine levels may possibly be caused, at least in part, by an elevation of endogenous SAM, a compound with mood-elevating properties.^{36,75} Whether the repetitive administration of SAM at oral doses effective for the treatment of major depressive disorder (1600 mg daily⁷⁶) causes an increase in homocysteine levels in individuals with major depressive disorder is unknown. However, a single dose of 400 mg of

SAM does not seem to be associated with an increase in homocysteine levels in healthy individuals.⁷⁷

Interestingly, an earlier open-label study⁷⁸ suggested that 6 weeks of folate supplementation at doses known to lower plasma homocysteine levels significantly (50 mg per day of oral methyltetrahydrofolate) without additional antidepressive agents is associated with potent antidepressive effects in elderly persons with DSM-III-R depressive disorder who are not folic acid deficient. In these patients, scores on the 21-item Hamilton Rating Scale for Depression were 34.8 ± 5.5 at baseline and 9.9 ± 10.8 at 6 weeks ($p < 0.0001$).

HOMOCYSTEINE, LIPID PEROXIDATION, AND OMEGA-3 FATTY ACIDS

A recent study in rats⁷⁹ provided interesting data regarding a possible link between hyperhomocysteinemia, lipid peroxidation, and omega-3 fatty acids. In this investigation an experimental group of Sprague-Dawley rats received a diet low in folic acid ($250 \mu\text{g}$ per kg of body weight), while a control group received a standard diet ($750 \mu\text{g}$ of folic acid per kg of body weight). After 6 weeks, the experimental group showed a 40% reduction in plasma folate concentration and a 32% reduction of folic acid in red blood cells, compared to the control group. Total plasma homocysteine was nearly fourfold higher in the experimental group than in the control group. Furthermore, plasma samples from folic acid-deficient rats contained significantly more products of lipid peroxidation (conjugated dienes, $p < 0.001$; thiobarbituric acid-reactive substances, $p < 0.001$; lipid peroxides, $p < 0.001$), and erythrocytes from these animals showed an enhanced susceptibility to free radicals in vitro ($p < 0.005$). In addition, the platelets showed a significant 27% decrease of total omega-3 fatty acids in the experimental group; the decrease was most significant ($p < 0.0001$) for ALA. Arachidonic acid (AA; an omega-6 fatty acid) was increased ($p < 0.01$), as was the AA/EPA quotient (45.45 compared to 31.25). Finally, in vitro markers of platelet activation (elevation of thromboxane in response to thrombin stimulation; $p < 0.002$) and platelet aggregation (after stimulation with low concentrations of thrombin or adenosine diphosphate; $p < 0.0002$ and < 0.0025 , respectively) were increased significantly more in the experimental group than in the controls. These results are in line with a recent study⁸⁰ in which the daily administration of methyltetrahydrofolate for 15 days significantly increased DHA ($p < 0.05$) in rat erythrocyte phospholipids compared to controls but did not induce significant changes in omega-6 fatty acid status.

These data strongly suggest that, at least in rats, elevated homocysteine levels (a graded independent risk factor for atherosclerosis in humans^{35,59,60}) initiate lipid peroxidation and thereby cause low tissue omega-3 fatty acids, a risk

TABLE 4. Studies of Homocysteine and Affective Disorders

Study	Subjects	Study design/methods	Results
Fava et al. ³⁸	213 drug-free outpatients with DSM-IV major depressive disorder and a mean baseline score of 19.6 (SD = 3.3) on the 17-item HAM-D and 48 healthy adult volunteers. Exclusion criteria: organic mental disorders, substance use disorders active in the previous year, clinical or laboratory evidence of hypothyroidism.	Clinical study of the relationships between levels of serum folate, vitamin B ₁₂ , and homocysteine and both depressive subtype and response to fluoxetine. Determination of severity (17-item HAM-D) and subtype of depression, levels of serum folate, vitamin B ₁₂ , and homocysteine.	Homocysteine levels were elevated (2 SDs above the comparison mean: 13.2–16.0 μmol/L) in 11% of the patients and high (3 SDs above the comparison mean: > 16.0 μmol/L) in 9%. The mean homocysteine level in the healthy adult volunteers was 7.3 μmol/L. Levels were not significantly related to any subtype of major depressive disorder, response status to 8 wk of 20 mg/d fluoxetine, gender, or age. Among the patients, 17% had low folate levels and 2% were folate deficient; 8% had low B ₁₂ levels and 4% were B ₁₂ deficient.
Bottiglieri et al. ³⁶	46 inpatients with DSM-III depression and HAM-D > 17 who had not been taking psychotropic medication for at least 1 wk, 20 patients with various neurological disorders, and 18 healthy normal volunteers. Exclusion criteria: drug or alcohol misuse, cognitive impairment, severe physical illness.	Controlled clinical study to determine whether plasma homocysteine is a more sensitive measure of functional folate than is serum or red cell folate assay. Severity of depression measured with HAM-D; in all 84 subjects, fasting blood samples were taken to determine full blood count, serum and RBC folate, serum vitamin B ₁₂ , and total plasma homocysteine. In 28 of the depressed patients and 17 of the neurological controls, fasting CSF samples were obtained to examine folate, SAM, 5HIAA, HVA, and MHPG.	None of the subjects was anemic or macrocytic. The mean serum vitamin B ₁₂ concentration was not significantly different in the depressed patients compared to the normal and neurological controls. Mean total plasma homocysteine concentration was 13.2 μmol/L in the depressed patients, compared with 7.6 μmol/L in the normal controls and 6.6 μmol/L in the neurological controls. In the depressed group, mean plasma total homocysteine concentration was significantly increased compared with normal ($t = 4.07, p < 0.01$) and neurological ($t = 5.02, p < 0.001$) controls, total plasma homocysteine was significantly correlated with RBC folate ($r = -0.50, n = 42, p < 0.01$), and unlike in the neurological control group, total plasma homocysteine was significantly negatively correlated with CSF SAM ($r = -0.399, n = 28, p < 0.05$). Of the depressed patients, 52.1% had a total plasma homocysteine concentration of ≥ 12 μmol/L, above the normal and neurological control range (3.4–11.9 μmol/L). In this high-homocysteine depressed subgroup, HAM-D scores were significantly higher than in the normal-homocysteine depressed subgroup ($t = 2.4, p < 0.01$) but were unrelated to RBC and serum folate concentrations; CSF folate ($t = 2.46, p < 0.02$) and mean CSF SAM ($t = 3.01, p < 0.01$), 5-HIAA ($t = 2.04, p < 0.05$), HVA ($t = 2.54, p < 0.02$), and MHPG concentrations ($t = 2.11, p < 0.04$) were significantly lower than in the neurological controls.

TABLE 4. Studies of Homocysteine and Affective Disorders (cont'd.)

Study	Subjects	Study design/methods	Results
Coppen & Bailey ³⁷	127 outpatients with DSM-III-R major depressive disorder and 17-item HAM-D score ≥ 20 who had not taken antidepressants during the previous 9 wk. Exclusion criteria: history of alcohol or drug abuse within the previous 6 mo; abnormalities on clinically relevant laboratory tests, including megaloblastic anemia.	10-wk double-blind, randomized, placebo-controlled trial in a multicenter general practice setting. Patients received 20 mg fluoxetine plus either 500 μ g folic acid or an identical-looking placebo. Plasma folate, homocysteine, and B ₁₂ levels were measured at baseline and 10 wk.	Baseline homocysteine concentration was 9.52 μ mol/L (SD = 3.22) in the fluoxetine/folic acid group, and 9.09 μ mol/L (SD = 2.79) in the fluoxetine/placebo group. At 10 wk, the fluoxetine/folic acid group showed significantly greater improvement in HAM-D scores than did the fluoxetine/placebo group ($p < 0.05$), but this superiority applied only to female patients ($p < 0.005$). Furthermore, in every other outcome comparison (patients recovered vs. the remainder; patients responding vs. the remainder; nonresponders vs. the remainder) the fluoxetine/folic acid group did better than the fluoxetine/placebo group; again, this was true only for female patients. The fluoxetine/folic acid group, but not the fluoxetine/placebo group, showed a significant ($p < 0.001$) decrease in homocysteine levels to 8.01 μ mol/L (SD = 2.23) at 10 wk compared with baseline. This was found in the women (from 9.46 μ mol/L [SD = 3.69] to 7.51 μ mol/L [SD = 1.63]; $p < 0.001$) but not in the men (from 9.65 μ mol/L [SD = 2.05] to 9.01 μ mol/L [SD = 2.90]). Plasma homocysteine concentration at 10 wk was significantly positively correlated with the 10-wk HAM-D score in the fluoxetine/folic acid group ($r = 0.391$, $p < 0.01$) but not in the fluoxetine/placebo group. Improvement was not related to plasma folate.

CSF, cerebrospinal fluid; *DSM*, Diagnostic and Statistical Manual of Mental Disorders; *HAM-D*, Hamilton Rating Scale for Depression; *5-HIAA*, 5-hydroxyindoleacetic acid; *HVA*, homovanillic acid; *MHPG*, 3-methoxy-4-hydroxyphenyl glycol; *RBC*, red blood cell; *SAM*, S-adenosylmethionine; *SD*, standard deviation.

factor for sudden cardiac death in humans.²⁹ Furthermore, they demonstrate that (at least in rats) administering folic acid, which at sufficient dosages lowers homocysteine levels, increases omega-3 polyunsaturated fatty acid tissue lipids. These findings very much resemble those from individuals with affective disorders. Low serum or red blood cell folic acid levels,³⁸ hyperhomocysteinemia,³⁶⁻³⁸ increased lipid peroxidation,^{32,39,54,81} low levels of tissue omega-3 fatty acids, an increased AA/EPA quotient,³⁰⁻³² and increased platelet activation⁸² have all been reported in patients with major depressive disorder. Successful standard antidepressant treatment does not seem to alter these factors, except for platelet activation.^{83,84} Preliminary data indicate that the increase in platelet activation in major depressive disorder is partly,⁸³ if

not totally,^{82,84} independent of the changes in parameters of primary hemostasis (heightened platelet activation, secretion, and aggregation) associated with metabolic risk factors for heart disease and stroke,⁸⁵ such as obesity⁸⁶ and hypertension.⁸⁷

DISCUSSION

The data presented in this paper suggest that elevated plasma homocysteine levels and a low intake of omega-3 fatty acids/reduced levels of omega-3 fatty acids may be risk factors for both major depressive disorder and cardiovascular disease. This shared pathophysiology could account, at least partly, for the increased risk of cardiovascular mortal-

ity in patients with depression. In patients with myocardial infarction, omega-3 fatty acids have been shown to decrease the risk of sudden cardiac death substantially. In patients at risk of or already afflicted by atherosclerosis, lowering homocysteine levels has been associated with an improvement of markers for coronary artery disease and cerebrovascular disease.

Antidepressants alone do not seem to increase omega-3 fatty acid levels or lower plasma homocysteine levels in patients with major depressive disorder, despite successful treatment of the mental symptoms of depression.^{37,39} Therefore, in addition to antidepressants, a supplementary treatment regimen of selected nutritional agents may be indicated. Such supplementation, if safe and effective, may reduce the high monetary and societal costs of depression, which are further increased when depression is comorbid with cardiovascular disease.⁸⁸

We propose that a double-blind placebo-controlled study comparing a second- or third-generation antidepressant with a homocysteine-lowering vitamin combination (folic acid plus vitamins B₆ and B₁₂) and omega-3 fatty acids in patients with major depressive disorder and myocardial infarction should be the first priority. This study should compare outcomes in four groups of patients, all of whom would be taking antidepressants: persons receiving/not receiving add-on vitamins, and persons receiving/not receiving add-on omega-3 fatty acids. Until such a study has been conducted and the results have been made available, the following suggestions might help as a preliminary treatment guide.

The American Heart Association's revised dietary guidelines⁴⁰ recommend that the general population consume at least two servings of fatty fish per week (no upper limit specified) to reduce the risk of cardiovascular disease. We suggest that every patient with major depressive disorder should also follow this advice. Alternatively, a Mediterranean ALA-rich diet should be implemented.⁴³ For patients who prefer to take supplements, ½–1 tablespoon of (preferably lignan-rich^{89–91}) flaxseed oil per day (3–6 g of ALA), or 1–2 g of EPA and DHA per day (found in fish oil), seems prudent and effective.

In clinical trials, 20–50% (depending on whether the cut-off level is set at 13.2 μmol/L³⁸ or 12 μmol/L³⁶) of patients with major depressive disorder have been demonstrated to have homocysteine levels associated with an increased risk of cardiovascular mortality (≥ 10 μmol/L⁹²). Because depressed individuals with comorbid conditions associated with high homocysteine, such as hypothyroidism,^{93–95} neurocognitive dysfunction,⁹⁶ or alcohol abuse,⁹⁷ were excluded from the study population, the actual prevalence of hyperhomocysteinemia among patients with major depressive disorder in clinical practice may be even higher. Therefore, patients with this disorder represent a “high-risk population,”

in which levels of fasting homocysteine should be determined.⁹² We therefore recommend that every patient with major depressive disorder have his or her homocysteine level checked. For patients found to have hyperhomocysteinemia (basal homocysteine ≥ 10 μmol/L),⁹² we suggest daily oral supplementation with folic acid (5 mg), vitamin B₆ (50 mg), and vitamin B₁₂ (1 mg). To keep costs low, we recommend one-time baseline homocysteine testing (\$75–\$127) and, in case of hyperhomocysteinemia, immediately proceeding with high-dose vitamin supplementation. Lowering homocysteine with folic acid (and vitamin B₆) seems to affect the evolution of arterial occlusive diseases favorably.^{62–65} Lowering homocysteine levels with folic acid has been found to enhance the antidepressant properties of fluoxetine.³⁷ The recommended daily vitamin combination, which includes folic acid, vitamin B₆, and—for safety reasons^{98,99}—vitamin B₁₂, will cost approximately \$10–15 per month.

LIMITATIONS OF THE ANALYSIS AND THE RECOMMENDATIONS

The major limitation of this analysis and the recommendations is the absence of controlled data examining the effects of omega-3 fatty acid supplementation and/or homocysteine-lowering vitamin therapy on cardiovascular morbidity and mortality in patients with major depressive disorder. Furthermore, it is not known whether reduction of plasma homocysteine will decrease cardiovascular mortality in patients with vascular disease. However, several large randomized controlled trials of homocysteine-lowering therapy (i.e., Bergen Vitamin Study, Cambridge Heart Antioxidant Study, Heart Outcomes Prevention Evaluation Study, Norwegian Study of Homocysteine Lowering with B-Vitamins in Myocardial Infarction, Prevention with a Combined Inhibitor and Folate in Coronary Heart Disease Study, Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine, Vitamins in Stroke Prevention Trial, Vitamins to Prevent Stroke Study, Women's Antioxidant and Cardiovascular Disease Study) are now under way to address this issue.⁶⁰

Evidence obtained from clinical trials does not always translate into valuable information when it comes to treating psychiatric patients, for many of these individuals would have been excluded from the pertinent trials.¹⁰⁰ However, the evidence regarding the cardiovascular effects of omega-3 fatty acids and homocysteine-lowering treatment obtained from clinical trials may provide valuable guidance for clinical practice. The secondary prevention trials of omega-3 fatty acids following an index myocardial infarction^{41–45} were add-on studies, with very few exclusionary criteria. The same applies to two of the three homocysteine-lowering controlled trials.^{62–64}

Finally, manuscripts reporting positive study results tend to be more frequently submitted and accepted than those reporting negative results.¹⁰¹ Because our study is based on a *Medline* search, we cannot exclude an inherent bias in our analysis.

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