Major Depressive Disorder Is Associated With Cardiovascular Risk Factors and Low Omega-3 Index

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ABSTRACT

Objective: Cardiovascular disease (CVD) and major depressive disorder (MDD) are frequent worldwide and have a high comorbidity rate. Omega-3 fatty acids have been suggested as disease modulators for both CVD and MDD. Therefore, we studied whether polyunsaturated fatty acids and the Omega-3 Index may represent markers for assessment of the cardiovascular risk in somatically healthy patients suffering from MDD.

Method: We conducted a case-control study from July 2004 to December 2007 in 166 adults (86 inpatients with MDD but without CVD from the Department of Psychiatry and Psychotherapy and 80 age- and sex-matched healthy controls from an outpatient clinic of the Division of Preventive Cardiology, Ludwig Maximilian University of Munich, Germany). Information gathered at baseline included MDD diagnosis according to *DSM-IV* criteria, depression ratings, conventional cardiovascular risk factors, and fatty acid and interleukin-6 determinations. Fatty acid composition was analyzed according to the HS-Omega-3 Index methodology. During the study, patients received no supplementation with omega-3 fatty acids. The main inclusion criteria were the diagnosis of MDD according to *DSM-IV* and a 17-item Hamilton Depression Rating Scale (HDRS-17) score of at least 17. Treatment response and remission were defined using the HDRS-17.

Results: Several conventional risk factors such as high triglyceride (mean, 152 mg/dL vs 100 mg/dL; $P < .001$) and fasting glucose (mean, 96 mg/dL vs 87 mg/dL; $P = .005$) values as well as greater waist circumference (mean, 97 cm vs 87 cm; $P = .019$) and higher body mass index (calculated as kg/m^2; mean, 26 vs 24; $P = .011$) were more prevalent in MDD patients in comparison with controls. The Omega-3 Index (mean, 3.9% vs 5.1%; $P < .001$) and individual omega-3 fatty acids were significantly lower in MDD patients. An Omega-3 Index < 4% was associated with high concentrations of the proinflammatory cytokine interleukin-6 ($\chi^2 = 7.8$, $P = .02$).

Conclusions: Conventional cardiovascular risk factors, the Omega-3 Index, and interleukin-6 levels indicated an elevated cardiovascular risk profile in MDD patients currently free of CVD. Our results support the employment of strategies to reduce the cardiovascular risk in still cardiovascularly healthy MDD patients by targeting conventional risk factors and the Omega-3 Index.

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Major depressive disorder (MDD) is recognized as a major risk factor for cardiovascular disease (CVD) and mortality after myocardial infarction,[1,2] independent of traditional risk factors.[3] A bidirectional relationship between the cardiovascular system and altered mood states related to an inflammatory status has been suggested.[4] Also, conventional cardiovascular risk factors are more prevalent in MDD patients, confirming the association between depression and CVD.[5] Consumption of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been inversely related to the occurrence of cardiovascular events such as atherosclerosis or arrythmias[6] and to the incidence of MDD.[7–12] Since EPA and DHA influence membrane fluidity, cytokine formation, and neurotransmission, they may play a role in the pathophysiology of MDD.[13] Moreover, EPA and DHA are required for human brain development[14] and may influence cellular aging by deceleration of telomere attrition[15] in general.

Large intervention studies in cardiovascular patients demonstrated reductions of serious clinical events with use of EPA and DHA,[16–18] but, also, studies without significant positive effects have been published recently.[19] Some, but not all, intervention studies demonstrated improved MDD after increased omega-3 fatty acid consumption.[7] Antidepressants,[20] or a combination of psychotherapy and selective serotonin reuptake inhibitors (SSRIs),[21] however, did not reduce the cardiovascular risk significantly. Even though the first study was designed and powered to demonstrate only antidepressant treatment effects, the results of both studies indicate the need for the investigation of new intervention strategies in larger studies.

The Omega-3 Index[22–25] represents an individual's status for levels of EPA and DHA. The Omega-3 Index is determined in erythrocytes using a standardized and reproducible assay.[25] Since the Omega-3 Index correlates inversely with risk for adverse cardiovascular events, particularly sudden cardiac death,[22,24,25] it has been suggested as a risk factor for cardiovascular events.[22–25] Vulnerabilities for MDD and other adverse neurodevelopmental[26–28] and neuropsychiatric[10] outcomes have also been linked to low levels of EPA and DHA. Whether a low Omega-3 Index indicates risk for MDD remained to be investigated.

In the present study, we investigated whether patients with MDD, but without CVD, differ in cardiovascular risk factors and in the Omega-3 Index from matched healthy controls. In an additional explorative analysis, we investigated the association between the proinflammatory cytokine interleukin-6 and the Omega-3 Index.

METHOD

Study Design and Participants

We recruited 100 patients with MDD from inpatients at the Department of Psychiatry and Psychotherapy and 104 healthy controls

from an outpatient clinic of the Division of Preventive Cardiology, Ludwig Maximilian University of Munich, Germany. Patients were diagnosed according to *DSM-IV* by experienced and trained psychiatrists using the Structured Clinical Interview for *DSM-IV* Axis I Disorders.[29] Only patients over 18 years of age with a depressive episode of at least moderate severity were included. The main inclusion criteria were unipolar depression and a score on the 17-item Hamilton Depression Rating Scale (HDRS-17)[30] of at least 17. Thirty-eight patients and controls were excluded due to somatic or psychiatric diagnoses detected after study inclusion, withdrawal of consent, and the procedure of exact matching for age and gender. Eighty-six patients and 80 controls remained in the final analysis.

Prior to the patients' inclusion in the study, blood samples were obtained for routine laboratory screening, a medical history was taken, and a physical examination was performed by a physician to exclude severe medical disorders. Clinically relevant medical illness (including diabetes mellitus or hyperlipidemia requiring treatment), neurologic illness, alcohol or drug abuse within the last 6 months prior to study inclusion (or withdrawal signs), and the concomitant use of antihypertensive medications such as angiotensin converting enzyme (ACE) inhibitors and β-blockers, as well as hormone replacement therapies, led to exclusion from the study. Due to application of the exclusion criteria, some risk factors of metabolic syndrome could be present, but a manifest metabolic syndrome according to World Health Organization[31] or International Diabetes Foundation[32] criteria was rare in both patients and controls. Exact dietary data were not assessed; the patients had free choice of 3 hospital meals, including the option, but not the obligation, to eat fish at least once a week.

After a washout period of at least 3 days prior to the blood sampling, the study patients received various antidepressant treatments. Changes in the depressive state were monitored using the HDRS-17, the Montgomery-Asberg Depression Rating Scale (MADRS),[33] the Beck Depression Inventory (BDI),[34] and the Clinical Global Impressions-Improvement (CGI-I) scale.[35] The primary criterion for treatment response was a 50% decline in the HDRS-17 sum score; remission was defined as an absolute HDRS-17 score below 7.

Mean ± SD age (MDD group vs controls: 49.9 ± 13.1 vs 50.6 ± 13.9 years) and gender distribution (61.6% male vs 62.5% female) showed no significant differences between groups. Psychiatric ratings indicated moderately severe depression in the MDD group (HDRS-17: 22.3 ± 5.4; MADRS: 32.7 ± 7.1; BDI: 26.8 ± 9.1; and CGI-I: 5.4 ± 0.52). The study was approved by the ethics committee of the medical faculty of Ludwig Maximilian University of Munich. Written informed consent was obtained from all patients and controls. The study was conducted from July 2004 to December 2007.

Procedures

In both groups, height and weight were measured and the body mass index was calculated (kg/m^2). Hip and waist circumference were measured to calculate the hip/waist ratio. At least 2 blood pressure determinations were made after the patient or control subject had been sitting for at least 5 minutes with the arm at heart level. Mean values were used for further analysis. Present and lifetime smoking status were assessed. Psychopharmacologic pretreatment was assessed. During the study, patients received various antidepressant treatments but no supplementation with omega-3 fatty acids.

Age- and sex-matched controls were recruited and screened for psychiatric and medical disorders. Only healthy individuals negative for both, as judged by trained specialists, entered the study. Blood samples for omega-3 fatty acid determinations were done at 8:00 AM and under fasting conditions at baseline and before discharge.

After centrifugation of 10 mL of whole blood, serum and erythrocytes were stored at −80°C. All measurements were performed twice by single-blinded personnel.

Lipid parameters were determined using laboratory routine methods, including the Friedewald formula. Erythrocyte fatty acid composition was analyzed according to the HS-Omega-3 Index methodology as previously described.[22] Fatty acid methyl esters were generated from erythrocytes by acid transesterification and analyzed by gas chromatography using a GC2010 Gas Chromatograph (Shimadzu Deutschland GmbH, Duisburg, Germany) equipped with an SP2560, 100-mm column (Supelco Inc, Bellefonte, Pennsylvania) using hydrogen as carrier gas. Fatty acids were identified by comparison with a standard mixture of fatty acids characteristic of erythrocytes. Results are given as EPA plus DHA expressed as a percentage of total identified fatty acids after response factor correction. The coefficient of variation for EPA plus DHA was 5%. High-sensitivity interleukin-6 concentrations were measured using ELISA assay kits (R&D Systems, Minneapolis, Minnesota) according to the protocol delivered from the manufacturer.

Statistical Analysis

All analyses were performed using SPSS for Windows, Version 15.0.1 (SPSS Inc, Chicago, Illinois). The 1-sample Kolmogorov-Smirnov test was used to test normal distribution of all variables. Because some variables were not normally distributed, nonparametric comparisons of mean values using the Mann-Whitney *U* test for comparison of independent samples (MDD vs controls) and the Wilcoxon signed rank test to detect differences in the distributions of 2 related variables (MDD before and after treatment) were used. In the case of normally distributed variables, Student *t* tests were used. In the case of categorical variables, the frequencies were compared using χ^2 tests. We subdivided patients and controls into 3 groups according to the established risk estimation for sudden cardiac death using the Omega-3 Index (< 4%, 4%–8%, > 8%) and detected differences in interleukin-6 concentrations between the groups using the nonparametric Kruskal-Wallis test. Presupposing an α of .05, a statistical power (Mann-Whitney *U* test) of > 0.90 for the detection of clinically relevant differences

between patients and healthy subjects could be reached with at least 80 patients per group. The level of significance was set at .05. Data are presented as mean ± SD in text or with standard error of the mean in Figure 2.

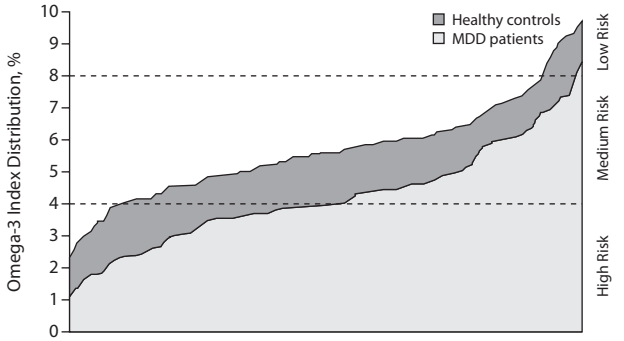
RESULTS

Depressed patients, in comparison with controls, had significantly higher triglycerides (152.4 ± 98.4 mg/dL vs 99.8 ± 49.6 mg/dL; $Z = -3.51$; $P < .001$), higher fasting glucose (96.4 ± 19.0 mg/dL vs 86.7 ± 12.5 mg/dL; $Z = -2.80$; $P = .005$), greater body mass index (25.6 ± 4.1 vs 24.0 ± 2.8; $Z = -2.56$; $P = .011$), greater waist circumference (96.8 ± 13.2 cm vs 87.4 ± 10.6 cm; $Z = -2.35$; $P = .019$), and lower high-density lipoprotein cholesterol (59.6 ± 17.3 mg/dL vs 67.8 ± 20.0 mg/dL; $Z = -2.40$; $P = .016$), indicating a higher risk for the metabolic syndrome in MDD. According to the International Diabetes Foundation criteria[32] for risk factors for the metabolic syndrome, elevated triglycerides exceeded the threshold of 150 mg/dL significantly more often in depressed patients ($\chi^2 = 10.9$, $P = .001$); the same was true for fasting glucose values above 100 mg/dL ($\chi^2 = 10.1$, $P = .001$), whereas high-density lipoprotein cholesterol was significantly more often too low ($\chi^2 = 4.9$, $P = .027$). The other risk factors, waist circumference and blood pressure, were not significantly different. The full diagnosis of the metabolic syndrome according to International Diabetes Foundation criteria[32] was present only in 2 patients and 2 controls; the distribution was therefore not significantly different in the 2 groups ($\chi^2 = 0.005$, $P = .94$).

Apparently, also, the psychopharmacologic pretreatment did not facilitate the development of the metabolic syndrome in more patients. Thirty-seven patients (43.0% of the MDD group) received no psychopharmacologic pretreatment at the time of inclusion into the study; 6 patients (7.0%) received atypical neuroleptics to augment antidepressant treatments. Four of those (4.7%) received aripiprazole, which is known to not significantly enhance the risk for development of the metabolic syndrome; 1 (1.2%) received risperidone, which is known to cause a moderate risk enhancement; and 1 (1.2%) received olanzapine, which is known to enhance the risk markedly. In addition, 33 patients (38.4%) were pretreated with antidepressants; 19 of those (22.1%) were treated with mirtazapine (n = 18, 20.9%) and/or amitriptyline (n = 2, 2.3%), both of which may enhance the risk for the metabolic syndrome due to their inherent antihistaminergic properties. The majority of the pretreated patients (n = 22, 25.6%) received a combination therapy of antidepressants with atypical neuroleptics or hypnotics; only 11 patients (12.8%) received monotherapy with antidepressants. Thirty-four of the depressed patients (39.5%), but only 14 of the healthy probands (17.5%), were actually smokers ($\chi^2 = 8.46$, $P = .004$).

The Omega-3 Index was normally distributed in both groups and was significantly lower in MDD patients in comparison to healthy controls (3.93% ± 1.50% vs 5.14% ± 1.38%, respectively; $t = -4.28$, $P < .001$) (Figure 1). In accordance with these findings, the distribution in predefined risk groups for sudden cardiac death was significantly different ($\chi^2 = 30.7$, $P < .001$) (Figure 1). When analyzed separately, EPA (0.98% ± 0.64% vs 1.31% ± 0.66%; $Z = -3.12$, $P = .002$), docosapentaenoic acid (1.54% ± 0.54% vs 1.90% ± 0.42%; $Z = -3.53$, $P < .001$), and DHA (2.96% ± 1.10% vs 3.84% ± 1.10%; $Z = -4.04$, $P < .001$) were also significantly lower in MDD patients.

Figure 1. Omega-3 Index Distribution in 86 MDD Patients and 80 Healthy Controls in Relation to Risk for Sudden Cardiac Death[a]



[a]Omega-3 Index distribution showing subdivision into 3 groups (< 4%, 4%–8%, and > 8%) according to risk stratification for sudden cardiac death. We presume that a significantly higher proportion of still cardiovascularly healthy MDD patients are at higher cardiovascular risk in comparison to healthy controls.
Abbreviation: MDD = major depressive disorder.

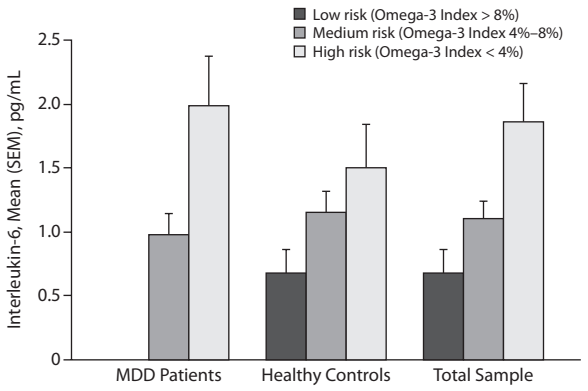
Successful treatment of depression (treatment response or remission), which did not include supplementation with omega-3 fatty acids, did not change omega-3 fatty acid levels in patients. Response to antidepressant treatment was evaluated at week 2, week 4, and at time of discharge. Responder status did not influence omega-3 fatty acids significantly, and vice versa. Only at the time point before discharge, a nonsignificant trend toward a higher Omega-3 Index could be found in treatment responders (responders vs nonresponders: 4.04% ± 1.06% vs 3.19% ± 1.42%; $t = -1.79$, $P = .083$). Time to response was 30.4 ± 23.3 days, time to remission was 38.4 ± 25.1 days, and time to discharge was 60.2 ± 50.6 days. After 4 weeks of treatment, 36 patients (41.9%) were treatment responders. During the week before discharge, 66 patients (76.7%) could be classified as treatment responders.

After subdivision of patients and controls into groups of high, medium, and low levels of the Omega-3 Index, lower levels were associated with significantly higher concentrations of the proinflammatory acute-phase cytokine interleukin-6 ($\chi^2 = 7.8$, $P = .02$) (Figure 2). The interleukin-6 levels at baseline were not correlated with HDRS-17 scores (Spearman $\rho = 0.14$, $P = .31$, not significant).

DISCUSSION

In the present study, we found an enhanced metabolic risk profile and a lower Omega-3 Index in cardiovascularly healthy MDD patients as compared to matched healthy controls. The present metabolic data may be caused by

Figure 2. Interleukin-6 Concentrations Are Inversely Associated With the Omega-3 Index[a]



[a]Concentrations of the proinflammatory cytokine interleukin-6 are significantly (Kruskal-Wallis test: $\chi^2_2 = 7.8$, $P = .02$) and inversely associated with the Omega-3 Index, a known risk factor for sudden cardiac death. The highest interleukin-6 concentrations could be observed in patients and controls with Omega-3 Index values below 4%, indicating antiinflammatory properties of EPA and DHA.
Abbreviations: DHA = docosahexaenoic acid, EPA = eicosapentaenoic acid, MDD = major depressive disorder.

unhealthy life styles (hypercaloric diet, low activity) and are therefore in line with reports about an association of such life styles with depressive symptoms,[36] but it remains a limitation of the presented study that no assessment of exact dietary data and daily activity was done. The smoking rates of about 39% in patients and 18% in healthy probands assessed in our study show deviation from mean values assessed by World Health Organization surveys within the time period of 2002–2006[37,38] indicating that a smoking rate of 27.4% within Germany and a rate of 28.6% within the European region could be found. An unhealthy lifestyle in our patients and, furthermore, a healthier-than-average life style in our healthy probands have therefore been confirmed, at least concerning smoking rate and also perhaps including nutritional factors. We therefore assume that our samples may be representative for depressed patients and for healthy, well-educated probands within a western European population. Nevertheless, local deviations may contribute to a relatively unhealthy diet, such as low fish consumption and subsequently low omega-3 fatty acid consumption in southern Bavaria in comparison to northern Germany or other northern European countries.

Previously, a low Omega-3 Index (< 4%) had been suggested as a risk factor for cardiovascular events, specifically for sudden cardiac death, whereas cardiovascular risk is thought to be minimal at levels between 8% and 11%.[22,39] Therefore, the increased cardiovascular risk in MDD patients might be related to and indicated by their low Omega-3 Index. In line with these findings, low levels of DHA were found in MDD patients, particularly in those suffering from acute CVD.[40–44] The level of the Omega-3 Index depends on a number of factors including intake of unsaturated fatty acids.[39] Therefore, in our study, dietary differences between the MDD patients and controls may be one reason for the significantly different status of the Omega-3 Index in the 2 samples.

Increasing the Omega-3 Index to levels between 8% and 11% might be an attractive approach to reduce the cardiovascular risk in MDD patients. This approach is supported by the results of large-scale intervention studies in cardiovascular patients[16] but remains to be demonstrated in separate investigations in MDD. In CVD patients suffering from depression, no beneficial effects of EPA and DHA supplementation on psychiatric outcome could be demonstrated.[19] Our study did not investigate MDD patients with manifest CVD and was not an interventional study. Therefore, our study can provide evidence for the usefulness of the Omega-3 Index only as a biological marker for cardiovascular risk in MDD and, possibly, also for MDD. Previous intervention studies did not recruit participants on the basis of their Omega-3 Index and did not find uniform effects of EPA and DHA.[7] Targeting MDD patients with a low Omega-3 Index might be a promising approach for future intervention studies with EPA and DHA, but these supposed beneficial effects remain to be demonstrated in further prospective clinical trials. Up to now, several randomized controlled trials[45–50] have demonstrated the superiority of adjunctive EPA or EPA/DHA combinations with antidepressants in the treatment of unipolar[45–48] or bipolar[49,50] depression, whereas EPA/DHA monotherapy has not been more efficacious than placebo treatment.[51] In addition, neutral studies using omega-3 fatty acids as an augmentation strategy with antidepressants,[52] with psychotherapy,[53] or as a relapse prevention strategy[54] have been published. One cause for neutral results may be the rapid and sustained improvement of mood due to the effectiveness of additional antidepressant treatments.[52,53] Nevertheless, several reviews and meta-analyses confirmed the efficacy of omega-3 fatty acids in the treatment of depression[7,43,55] but demanded further research due to the significant heterogeneity among published studies.[55–57]

Our data do not address the discussion of which omega-3 fatty acids (EPA, DHA, or combinations) and which dosages should be used in such studies.

The Omega-3 Index was lower in MDD patients than in controls. Previously, both decreased omega-3 fatty acid consumption[58] and low levels of omega-3 fatty acids[10,41–44] were found to be associated with depressive disorders. Chronic emotional stress seems to increase degradation of long-chain polyunsaturated fatty acids.[58] In addition, the frequent nicotine abuse in our patient group may have contributed to the lower Omega-3 Index because levels of omega-3 fatty acids are found to be lower in smokers than in nonsmokers.[59,60]

Our data are descriptive and thus do not clarify whether low intake, increased degradation, or other effects lead to a low Omega-3 Index. This question should be addressed in further studies. However, our data indicate that a low Omega-3 Index might also be a risk indicator for MDD. After successful antidepressant treatment that did not include omega-3 fatty acid supplementation, fatty acid levels

remained unchanged. Given the half-life of circulating red blood cells, the mean treatment interval until clinical response was achieved seems to be too short to influence omega-3 fatty acid concentrations significantly. This finding is in line with the results of intervention studies, which could not demonstrate an influence of antidepressant treatment such as SSRIs, or a combination of SSRIs with psychotherapy, on cardiovascular risk.[20,21] Levels of proinflammatory interleukin-6 were inversely related to the Omega-3 Index. This finding further supports the high risk for CVD and sudden cardiac death in MDD,[61] together with the high inflammatory activity in MDD[2] confirming potential anti-inflammatory properties of EPA and DHA.

In conclusion, we found more pronounced conventional risk factors, lower proportions of polyunsaturated fatty acids, and a lower Omega-3 Index in MDD patients as compared to matched controls, which explains the increased cardiovascular risk of MDD patients at least to some extent. We therefore suggest a new approach for intervention studies using omega-3 fatty acids or omega-3 fatty acid–rich diets to reduce the cardiovascular risk of MDD patients preemptively and to augment antidepressive treatment, and we also suggest including lifestyle interventions. Moreover, a low Omega-3 Index (< 4%) might also be a risk factor or a novel biological risk marker for MDD.

Drug names: aripiprazole (Abilify), mirtazapine (Remeron and others), olanzapine (Zyprexa), risperidone (Risperdal and others).

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Potential conflicts of interest: **Dr von Schacky** has received speaking honoraria from Solvay and is the founder of Omegametrix, Martinsried, Germany, a laboratory specializing in fatty-acid analyses. **Drs Baghai**, **Varallo-Bedarida**, **Born**, **Häfner**, **Schüle**, **Eser**, **Rupprecht**, and **Bondy** have no financial or other conflict of interest relevant to the subject matter of this article.

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REFERENCES

1. Frasure-Smith N, Lespérance F, Talajic M. Depression following myocardial infarction. Impact on 6-month survival. *JAMA*. 1993;270(15):1819–1825.
2. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry*. 1998;55(7):580–592.
3. Barefoot JC, Schroll M. Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation*. 1996;93(11):1976–1980.
4. Grippo AJ, Johnson AK. Biological mechanisms in the relationship between depression and heart disease. *Neurosci Biobehav Rev*. 2002;26(8):941–962.
5. Richter N, Juckel G, Assion HJ. Metabolic syndrome: a follow-up study of acute depressive inpatients. *Eur Arch Psychiatry Clin Neurosci*; 2010;260(1):41–49.
6. Kris-Etherton PM, Harris WS, Appel LJ; AHA Nutrition Committee, American Heart Association. Omega-3 fatty acids and cardiovascular disease: new recommendations from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2003;23(2):151–152.
7. Freeman MP, Hibbeln JR, Wisner KL, et al. Omega-3 fatty acids: evidence basis for treatment and future research in psychiatry. *J Clin Psychiatry*. 2006;67(12):1954–1967.
8. Freeman MP. Omega-3 fatty acids in major depressive disorder. *J Clin Psychiatry*. 2009;70(suppl 5):7–11.
9. Hibbeln JR. Fish consumption and major depression. *Lancet*. 1998; 351(9110):1213.
10. Maes M, Christophe A, Delanghe J, et al. Lowered omega3 polyunsaturated fatty acids in serum phospholipids and cholesteryl esters of depressed patients. *Psychiatry Res*. 1999;85(3):275–291.
11. Tanskanen A, Hibbeln JR, Tuomilehto J, et al. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv*. 2001;52(4):529–531.
12. Tanskanen A, Hibbeln JR, Hintikka J, et al. Fish consumption, depression, and suicidality in a general population. *Arch Gen Psychiatry*. 2001;58(5):512–513.
13. Colin A, Reggers J, Castronovo V, et al. Lipids, depression and suicide. *Encephale*. 2003;29(1):49–58.
14. Clandinin MT. Brain development and assessing the supply of polyunsaturated fatty acid. *Lipids*. 1999;34(2):131–137.
15. Farzaneh-Far R, Lin J, Epel ES, et al. Association of marine omega-3 fatty acid levels with telomeric aging in patients with coronary heart disease. *JAMA*. 2010;303(3):250–257.
16. Marchioli R, Levantesi G, Silletta MG, et al; GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids and rosuvastatin in patients with heart failure: results of the GISSI-HF trial. *Expert Rev Cardiovasc Ther*. 2009;7(7):735–748.
17. Gapinski JP, VanRuiswyk JV, Heudebert GR, et al. Preventing restenosis with fish oils following coronary angioplasty: a meta-analysis. *Arch Intern Med*. 1993;153(13):1595–1601.
18. von Schacky C. n-3 fatty acids and the prevention of coronary atherosclerosis. *Am J Clin Nutr*. 2000;71(suppl):224S–227S.
19. Carney RM, Freedland KE, Rubin EH, et al. Omega-3 augmentation of sertraline in treatment of depression in patients with coronary heart disease: a randomized controlled trial. *JAMA*. 2009;302(15):1651–1657.
20. Glassman AH, O'Connor CM, Califf RM, et al; Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group. Sertraline treatment of major depression in patients with acute MI or unstable angina. *JAMA*. 2002;288(6):701–709.
21. Berkman LF, Blumenthal J, Burg M, et al; Enhancing Recovery in Coronary Heart Disease Patients Investigators (ENRICHD). Effects of treating depression and low perceived social support on clinical events after myocardial infarction: the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) randomized trial. *JAMA*. 2003;289(23):3106–3116.
22. Harris WS, von Schacky C. The Omega-3 Index: a new risk factor for death from coronary heart disease? *Prev Med*. 2004;39(1):212–220.
23. Harris WS. The Omega-3 Index as a risk factor for coronary heart disease. *Am J Clin Nutr*. 2008;87(6):1997S–2002S.
24. Harris WS. The Omega-3 Index: from biomarker to risk marker to risk factor. *Curr Atheroscler Rep*. 2009;11(6):411–417.
25. Harris WS, Thomas RM. Biological variability of blood omega-3 biomarkers. *Clin Biochem*. 2010;43(3):338–340.
26. Williams C, Birch EE, Emmett PM, et al; Avon Longitudinal Study of Pregnancy and Childhood Study Team. Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study. *Am J Clin Nutr*. 2001;73(2):316–322.
27. Koletzko B, Lien E, Agostoni C, et al; World Association of Perinatal Medicine Dietary Guidelines Working Group. The roles of long-chain polyunsaturated fatty acids in pregnancy, lactation and infancy: review of current knowledge and consensus recommendations. *J Perinat Med*. 2008;36(1):5–14.
28. Willatts P, Forsyth JS, DiModugno MK, et al. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet*. 1998;352(9129):688–691.
29. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for* DSM-IV *Axis I Disorders*. Washington, DC: American Psychiatric Press; 1996.
30. Hamilton M. Development of a rating scale for primary depressive illness. *Br J Soc Clin Psychol*. 1967;6(4):278–296.
31. World Health Organization. Definition and diagnosis of diabetes mellitus

and intermediate hyperglycemia. 2006. http://www.idf.org/webdata/docs/WHO_IDF_definition_diagnosis_of_diabetes.pdf. Verified September 14, 2010.
32. International Diabetes Foundation. The IDF consensus worldwide definition of the metabolic syndrome. 2006. http://www.idf.org/webdata/docs/MetS_def_update2006.pdf. Verified September 14, 2010.
33. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
34. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4:561–571.
35. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
36. Bonnet F, Irving K, Terra JL, et al. Depressive symptoms are associated with unhealthy lifestyles in hypertensive patients with the metabolic syndrome. *J Hypertens*. 2005;23(3):611–617.
37. World Health Organization. *The European Tobacco Control Report 2007*. Copenhagen, Denmark: World Health Organization; 2007.
38. World Health Organization. *The European Health Report 2009: Health and Health Systems*. Copenhagen, Denmark: World Health Organization; 2009.
39. von Schacky C. Use of red blood cell fatty-acid profiles as biomarkers in cardiac disease. *Biomark Med*. 2009;3(1):25–32.
40. Parker GB, Heruc GA, Hilton TM, et al. Low levels of docosahexaenoic acid identified in acute coronary syndrome patients with depression. *Psychiatry Res*. 2006;141(3):279–286.
41. Edwards R, Peet M, Shay J, et al. Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord*. 1998;48(2-3):149–155.
42. Maes M, Smith R, Christophe A, et al. Fatty acid composition in major depression: decreased omega 3 fractions in cholesteryl esters and increased C20: 4 omega 6/C20:5 omega 3 ratio in cholesteryl esters and phospholipids. *J Affect Disord*. 1996;38(1):35–46.
43. Parker G, Gibson NA, Brotchie H, et al. Omega-3 fatty acids and mood disorders. *Am J Psychiatry*. 2006;163(6):969–978.
44. Peet M, Murphy B, Shay J, et al. Depletion of omega-3 fatty acid levels in red blood cell membranes of depressive patients. *Biol Psychiatry*. 1998; 43(5):315–319.
45. Su KP, Huang SY, Chiu TH, et al. Omega-3 fatty acids for major depressive disorder during pregnancy: results from a randomized, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2008;69(4):644–651.
46. Su KP, Huang SY, Chiu CC, et al. Omega-3 fatty acids in major depressive disorder: a preliminary double-blind, placebo-controlled trial. *Eur Neuropsychopharmacol*. 2003;13(4):267–271.
47. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Arch Gen Psychiatry*. 2002;59(10):913–919.
48. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002;159(3):477–479.
49. Stoll AL, Severus WE, Freeman MP, et al. Omega 3 fatty acids in bipolar disorder: a preliminary double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1999;56(5):407–412.
50. Frangou S, Lewis M, McCrone P. Efficacy of ethyl-eicosapentaenoic acid in bipolar depression: randomised double-blind placebo-controlled study. *Br J Psychiatry*. 2006;188(1):46–50.
51. Marangell LB, Martinez JM, Zboyan HA, et al. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. *Am J Psychiatry*. 2003;160(5):996–998.
52. Silvers KM, Woolley CC, Hamilton FC, et al. Randomised double-blind placebo-controlled trial of fish oil in the treatment of depression. *Prostaglandins Leukot Essent Fatty Acids*. 2005;72(3):211–218.
53. Freeman MP, Davis M, Sinha P, et al. Omega-3 fatty acids and supportive psychotherapy for perinatal depression: a randomized placebo-controlled study. *J Affect Disord*. 2008;110(1-2):142–148.
54. Marangell LB, Martinez JM, Zboyan HA, et al. Omega-3 fatty acids for the prevention of postpartum depression: negative data from a preliminary, open-label pilot study. *Depress Anxiety*. 2004;19(1):20–23.
55. Lin PY, Su KP. A meta-analytic review of double-blind, placebo-controlled trials of antidepressant efficacy of omega-3 fatty acids. *J Clin Psychiatry*. 2007;68(7):1056–1061.
56. Montgomery P, Richardson AJ. Omega-3 fatty acids for bipolar disorder. *Cochrane Database Syst Rev*. 2008;(2):CD005169.
57. Kraguljac NV, Montori VM, Pavuluri M, et al. Efficacy of omega-3 fatty acids in mood disorders: a systematic review and meta-analysis. *Psychopharmacol Bull*. 2009;42(3):39–54.
58. Hibbeln JR, Salem N Jr. Dietary polyunsaturated fatty acids and depression: when cholesterol does not satisfy. *Am J Clin Nutr*. 1995;62(1):1–9.
59. Leng GC, Smith FB, Fowkes FG, et al. Relationship between plasma essential fatty acids and smoking, serum lipids, blood pressure and haemostatic and rheological factors. *Prostaglandins Leukot Essent Fatty Acids*. 1994;51(2):101–108.
60. Leng GC, Horrobin DF, Fowkes FG, et al. Plasma essential fatty acids, cigarette smoking, and dietary antioxidants in peripheral arterial disease. A population-based case-control study. *Arterioscler Thromb*. 1994;14(3):471–478.
61. Leonard BE, Myint A. The psychoneuroimmunology of depression. *Hum Psychopharmacol*. 2009;24(3):165–175.