Depression and Nutrition ~ Abstracts

Adams, P. B., S. Lawson, et al. (1996). "Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression." Lipids 31 Suppl: S157-61.

In this study of 20 moderately to severely depressed patients, diagnosed using current research diagnostic criteria and excluding known bipolar affective disorder and reactive depression, we investigated relationships between severity of depression and levels and ratios of n-3 and n-6 long-chain polyunsaturated fatty acids (PUFA) in plasma and erythrocyte phospholipids (PL). Severity of depression was measured using the 21-item Hamilton depression rating scale (HRS) and a second linear rating scale (LRS) of severity of depressive symptoms that omitted anxiety symptoms. There was a significant correlation between the ratio of erythrocyte PL arachidonic acid (AA) to eicosapentaenoic acid (EPA) and severity of depression as rated by the HRS ($P < 0.05$) and the LRS for depression ($P < 0.01$). There was also a significant negative correlation between erythrocyte EPA and the LRS ($P < 0.05$). The AA/EPA ratio in plasma PL and the ratio of erythrocyte long-chain (C20 and C22 carbon) n-6 to long-chain n-3 PUFA were also significantly correlated with the LRS ($P < 0.05$). These findings do not appear to be simply explained by differences in dietary intake of EPA. We cannot determine whether the high ratios of AA/EPA in both plasma and erythrocyte PL are the result of depression or whether tissue PUFA change predate the depressive symptoms. We suggest, however, that our findings provide a basis for studying the effect of the nutritional supplementation of depressed subjects, aimed at reducing the AA/EPA ratio in tissues and severity of depression.

Alesci, S., P. E. Martinez, et al. (2005). "Major Depression Is Associated with Significant Diurnal Elevations in Plasma Interleukin-6 Levels, a Shift of Its Circadian Rhythm, and Loss of Physiological Complexity in Its Secretion: Clinical Implications." J Clin Endocrinol Metab 90(5): 2522-2530.

Background: Major depressive disorder (MDD) is associated with increased risk for premature coronary heart disease and bone loss. Single time measurements of plasma IL-6, a good predictor of future risk for both cardiovascular disease and osteoporosis, revealed significant elevations in depressed patients. The objective of this study was to rigorously compare plasma IL-6 levels, measured over 24 h, in MDD patients and healthy controls. Given the activating role of IL-6 on the hypothalamic-pituitary-adrenal (HPA) axis, and the relevance of its dysregulation in MDD, we also analyzed the relations between IL-6 and cortisol levels. Methods: We studied nine patients and nine controls, individually matched by gender, age ({+/-}5 yr), body mass index ({+/-}2 kg/m2), and menstrual cycle phase. Diagnosis of MDD was confirmed by structured clinical interview based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I diagnostic criteria. Self-reported mood ratings were assessed by multiple visual analog scales. The rhythmicity and complexity of IL-6 and cortisol secretion were tested by cosinor analyses, approximate entropy (ApEn) and cross-ApEn algorithms. Results: MDD patients had significant mean IL-6 elevations from 1000-1200 h and at 1500 h (P ranging from <0.05 to <0.01) vs. controls. In addition, in MDD, the circadian rhythm of IL-6 was shifted by 12 h, and its physiological complexity was reduced, with no difference in the cross-ApEn of IL-6 and cortisol between the two groups, and significant time-lagged correlations only in the controls. IL-6 levels correlated significantly with mood ratings. Conclusions: We report profound morning elevations of plasma IL-6 and a reversal of its circadian rhythm in MDD patients, in the absence of hypercortisolism. These findings may be relevant to the increased risk for coronary heart disease and bone loss in MDD.

Arora, S. K. and S. I. McFarlane (2005). "The case for low carbohydrate diets in diabetes management." Nutr Metab (Lond) 2: 16.

A low fat, high carbohydrate diet in combination with regular exercise is the traditional recommendation for treating diabetes. Compliance with these lifestyle modifications is less than satisfactory, however, and a high carbohydrate diet raises postprandial plasma glucose and insulin secretion, thereby increasing risk of CVD, hypertension, dyslipidemia, obesity and diabetes. Moreover, the current epidemic of diabetes and obesity has been, over the past three decades, accompanied by a significant decrease in fat consumption and an increase in carbohydrate consumption. This apparent failure of the traditional diet, from a public health point of view, indicates that alternative dietary approaches are needed. Because carbohydrate is the major secretagogue of insulin, some form of carbohydrate restriction is a prima facie candidate for dietary control of diabetes. Evidence from various randomized controlled trials in recent years has convinced us that such diets are safe and effective, at least in short-term. These data show low carbohydrate diets to be comparable or better than traditional low fat

high carbohydrate diets for weight reduction, improvement in the dyslipidemia of diabetes and metabolic syndrome as well as control of blood pressure, postprandial glycemia and insulin secretion. Furthermore, the ability of low carbohydrate diets to reduce triglycerides and to increase HDL is of particular importance. Resistance to such strategies has been due, in part, to equating it with the popular Atkins diet. However, there are many variations and room for individual physician planning. Some form of low carbohydrate diet, in combination with exercise, is a viable option for patients with diabetes. However, the extreme reduction of carbohydrate of popular diets (<30 g/day) cannot be recommended for a diabetic population at this time without further study. On the other hand, the dire objections continually raised in the literature appear to have very little scientific basis. Whereas it is traditional to say that more work needs to be done, the same is true of the assumed standard low fat diets which have an ambiguous record at best. We see current trends in the national dietary recommendations as a positive sign and an appropriate move in the right direction.

Beard, J. L., M. K. Hendricks, et al. (2005). "Maternal Iron Deficiency Anemia Affects Postpartum Emotions and Cognition." J. Nutr. 135(2): 267-272.

The aim of this study was to determine whether iron deficiency anemia (IDA) in mothers alters their maternal cognitive and behavioral performance, the mother-infant interaction, and the infant's development. This article focuses on the relation between IDA and cognition as well as behavioral affect in the young mothers. This prospective, randomized, controlled, intervention trial was conducted in South Africa among 3 groups of mothers: nonanemic controls and anemic mothers receiving either placebo (10 {micro}g folate and 25 mg vitamin C) or daily iron (125 mg FeS04, 10 {micro}g folate, 25 mg vitamin C). Mothers of full-term normal birth weight babies were followed from 10 wk to 9 mo postpartum (n = 81). Maternal hematologic and iron status, socioeconomic, cognitive, and emotional status, mother-infant interaction, and the development of the infants were assessed at 10 wk and 9 mo postpartum. Behavioral and cognitive variables at baseline did not differ between iron-deficient anemic mothers and nonanemic mothers. However, iron treatment resulted in a 25% improvement ($P < 0.05$) in previously iron-deficient mothers' depression and stress scales as well as in the Raven's Progressive Matrices test. Anemic mothers administered placebo did not improve in behavioral measures. Multivariate analysis showed a strong association between iron status variables (hemoglobin, mean corpuscular volume, and transferrin saturation) and cognitive variables (Digit Symbol) as well as behavioral variables (anxiety, stress, depression). This study demonstrates that there is a strong relation between iron status and depression, stress, and cognitive functioning in poor African mothers during the postpartum period. There are likely ramifications of this poorer "functioning" on mother-child interactions and infant development, but the constraints around this relation will have to be defined in larger studies.

Bell, I. R., J. S. Edman, et al. (1991). "B complex vitamin patterns in geriatric and young adult inpatients with major depression." J Am Geriatr Soc 39(3): 252-7.

This study compared the B complex vitamin status at time of admission of 20 geriatric and 16 young adult non-alcoholic inpatients with major depression. Twenty-eight percent of all subjects were deficient in B2 (riboflavin), B6 (pyridoxine), and/or B12 (cobalamin), but none in B1 (thiamine) or folate. The geriatric sample had significantly higher serum folate levels. Psychotic depressives had lower B12 than did non-psychotic depressives. Poorer blood vitamin status was not associated with higher scores on the Hamilton Depression Rating Scale or lower scores on the Mini-Mental State Examination in either age group. The data support the hypothesis that poorer status in certain B vitamins is present in major depression, but blood measures may not reflect central nervous system vitamin function or severity of affective syndromes as measured by the assays and scales in the present study.

Bjelland, I., G. S. Tell, et al. (2003). "Folate, Vitamin B12, Homocysteine, and the MTHFR 677C->T Polymorphism in Anxiety and Depression: The Hordaland Homocysteine Study." Arch Gen Psychiatry 60(6): 618-626.

Background An association between depression and folate status has been demonstrated in clinical studies, whereas data are sparse on the relationship between depression and other components of 1-carbon metabolism such as vitamin B12, homocysteine, and the methylenetetrahydrofolate reductase 677C[-&gt]T polymorphism. The relationship between anxiety and these components is less well known. This study examined the associations between folate, total homocysteine, vitamin B12, and the methylenetetrahydrofolate reductase 677C[-&gt]T polymorphism, and anxiety and depression in a large

population-based study. Methods Anxiety and depression, measured by the Hospital Anxiety and Depression Scale, were assessed in 5948 subjects aged 46 to 49 years (mean, 47.4 years) and 70 to 74 years (mean, 71.9 years) from the Hordaland Homocysteine Study cohort. By means of logistic regression models, anxiety and depression scores were examined in relation to the factors listed above. Results Overall, hyperhomocysteinemia (plasma total homocysteine level >=15.0 {micro}mol/L [>=2.02 mg/dL]) (odds ratio, 1.90; 95% confidence interval, 1.11-3.25) and T/T methylenetetrahydrofolate reductase genotype (odds ratio, 1.69; 95% confidence interval, 1.09-2.62), but not low plasma folate or vitamin B12 levels, were significantly related to depression without comorbid anxiety disorder. Plasma folate level was inversely associated with depression only in the subgroup of middle-aged women. None of the investigated parameters showed a significant relationship to anxiety. Conclusion Our results provide further evidence of a role of impaired 1-carbon metabolism in depression.

Black, M. M. (2003). "Micronutrient Deficiencies and Cognitive Functioning." J. Nutr. 133(11): 3927S-3931.
The relationship between four micronutrient deficiencies (iodine, iron, zinc and vitamin B-12) and children's cognitive functioning is reviewed. Iodine deficiency during pregnancy has negative and irreversible effects on the developing fetus. Although there is some evidence that postnatal iodine deficiency is associated with cognitive deficits, the findings are controversial. Iron deficiency is widespread and has been associated to cognitive deficits, but the results of prevention trials are inconsistent. Zinc deficiency has been linked with low activity and depressed motor development among the most vulnerable children. Associations with cognitive development are less clear and may be limited to specific neuropsychological processes. Vitamin B-12 deficiency has been associated with cognitive problems among the elderly, but little is known about its effect on children's cognitive functioning. Rates of vitamin B-12 deficiency are likely to be high because animal products are the only source of vitamin B-12. Although micronutrient deficiencies often co-occur in the context of poverty, little is known about the impact of multiple micronutrient deficiencies on cognitive development.

Bodnar, L. M. and K. L. Wisner (2005). "Nutrition and depression: implications for improving mental health among childbearing-aged women." Biol Psychiatry 58(9): 679-85.
Adequate nutrition is needed for countless aspects of brain functioning. Poor diet quality, ubiquitous in the United States, may be a modifiable risk factor for depression. The objective was to review and synthesize the current knowledge of the role of nutrition in depression, and address implications for childbearing-aged women. Poor omega-3 fatty acid status increases the risk of depression. Fish oil and folic acid supplements each have been used to treat depression successfully. Folate deficiency reduces the response to antidepressants. Deficiencies of folate, vitamin B12, iron, zinc, and selenium tend to be more common among depressed than nondepressed persons. Dietary antioxidants have not been studied rigorously in relation to depression. Childbearing-aged women are particularly vulnerable to the adverse effects of poor nutrition on mood because pregnancy and lactation are major nutritional stressors to the body. The depletion of nutrient reserves throughout pregnancy and a lack of recovery postpartum may increase a woman's risk of depression. Prospective research studies are needed to clarify the role of nutrition in the pathophysiology of depression among childbearing-aged women. Greater attention to nutritional factors in mental health is warranted given that nutrition interventions can be inexpensive, safe, easy to administer, and generally acceptable to patients.

Bottiglieri, T., M. Laundy, et al. (2000). "Homocysteine, folate, methylation, and monoamine metabolism in depression." J Neurol Neurosurg Psychiatry 69(2): 228-232.
OBJECTIVES[---]Previous studies suggest that folate deficiency may occur in up to one third of patients with severe depression, and that treatment with the vitamin may enhance recovery of the mental state. There are, however, difficulties in interpreting serum and red cell folate assays in some patients, and it has been suggested that total plasma homocysteine is a more sensitive measure of functional folate (and vitamin B12) deficiency. Other studies suggest a link between folate deficiency and impaired metabolism of serotonin, dopamine, and noradrenaline (norepinephrine), which have been implicated in mood disorders. A study of homocysteine, folate, and monoamine metabolism has, therefore, been undertaken in patients with severe depression. METHODS[---]In 46 inpatients with severe DSM III depression, blood counts, serum and red cell folate, serum vitamin B12, total plasma homocysteine, and, in 28 patients, CSF folate, S-adenosylmethionine, and the monoamine neurotransmitter metabolites 5HIAA, HVA, and MHPG were examined. Two control groups comprised 18 healthy

volunteers and 20 patients with neurological disorders, the second group undergoing CSF examination for diagnostic purposes. RESULTS[---]Twenty four depressed patients (52%) had raised total plasma homocysteine. Depressed patients with raised total plasma homocysteine had significant lowering of serum, red cell, and CSF folate, CSF S-adenosylmethionine and all three CSF monoamine metabolites. Total plasma homocysteine was significantly negatively correlated with red cell folate in depressed patients, but not controls. CONCLUSIONS[---]Utilising total plasma homocysteine as a sensitive measure of functional folate deficiency, a biological subgroup of depression with folate deficiency, impaired methylation, and monoamine neurotransmitter metabolism has been identified. Detection of this subgroup, which will not be achieved by routine blood counts, is important in view of the potential benefit of vitamin replacement.

Bourre, J. M. (2005). "Dietary omega-3 Fatty acids and psychiatry: mood, behaviour, stress, depression, dementia and aging." J Nutr Health Aging 9(1): 31-8.

In view of the high omega-3 poly unsaturated fatty acid content of the brain, it is evident that these fats are involved in brain biochemistry, physiology and functioning; and thus in some neuropsychiatric diseases and in the cognitive decline of ageing. Though omega-3 fatty acids (from fatty fish in the human diet) appear effective in the prevention of stress, their role as regulator of mood and of libido is a matter for discussion pending experimental proof in animal and human models. Dietary omega-3 fatty acids play a role in the prevention of some disorders including depression, as well as in dementia, particularly Alzheimer's disease. Their direct role in major depression, bipolar disorder (manic-depressive disease) and schizophrenia is not yet established. Their deficiency can prevent the renewal of membranes, and thus accelerate cerebral ageing; none the less, the respective roles of the vascular component on one hand (where the omega-3's are active) and the cerebral parenchyma itself on the other, have not yet been clearly resolved. The role of omega-3 in certain diseases such as dyslexia and autism is suggested. In fact, omega-3 fatty acids participated in the first coherent experimental demonstration of the effect of dietary substances (nutrients) on the structure and function of the brain. Experiments were first of all carried out one x-vivo cultured brain cells (1), then on in vivo brain cells(2), finally on physiochemical, biochemical, physiological, neurosensory, and behavioural parameters (3). These findings indicated that the nature of poly unsaturated fatty acids(in particular omega-3) present in formula milks for infants (both premature and term) determines the visual, cerebral,and intellectual abilities, as described in a recent review (4). Indeed,the insufficient dietary supply of omega-3 fatty acids in today's French and occidental diet raises the problem of how to correct dietary habits so that the consumer will select foods that are genuinely rich in omega-3/ the omega-3 family; mainly rapeseed, (canola) and walnut oils on one hand and fatty fish on the other.

Brouwer, J. P., B. C. Appelhof, et al. (2005). "Thyroid and adrenal axis in major depression: a controlled study in outpatients." Eur J Endocrinol 152(2): 185-191.

Objective: Major depressive disorder has been associated with changes in the hypothalamus-pituitary-thyroid (HPT) axis and with hypercortisolism. However, the changes reported have been at variance, probably related to in- or outpatient status, the use of antidepressant medication and the heterogeneity of depression. We therefore conducted a controlled study in unipolar depressed outpatients who had been free of antidepressants for at least 3 months. Design: We assessed endocrine parameters in 113 depressed outpatients and in 113 sex- and age-matched controls. Methods: Patients were included if they had a major depression according to a Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM), fourth edition (SCID-IV) and if they had a 17-item Hamilton rating scale for depression (HRSD) score of [&ge]16. Endocrine parameters contained serum concentrations of TSH, (free) thyroxine, tri-iodothyronine, cortisol, thyroid peroxidase (TPO) antibody titre and 24-h urinary excretion of cortisol. Results: The serum concentration of TSH was slightly higher in depressed patients as compared with controls ($P < 0.001$), independent of the presence of subclinical hypothyroidism and/or TPO antibodies ($n = 28$). All other HPT axis parameters were similar in both groups. The 24-h urinary cortisol excretion was similar in patients and controls. In atypical depression, serum cortisol was lower than in non-atypical depression ($P = 0.01$). Patients with neither melancholic depression nor severe depression (HRSD [&ge]23) had altered endocrine parameters. Finally, serum TSH values could not be related to cortisol values. Conclusion: When compared with matched control subjects, outpatients with major depression had slightly higher serum TSH, while urinary cortisol levels were similar. Furthermore, we observed lower serum cortisol in atypical depression than in non-atypical depression.

Brown, L. C., S. R. Majumdar, et al. (2005). "History of Depression Increases Risk of Type 2 Diabetes in Younger Adults." Diabetes Care 28(5): 1063-1067.

OBJECTIVE--The purpose of this study was to assess the history of previous depression in people with incident diabetes compared with people without diabetes. RESEARCH DESIGN AND METHODS--We conducted a population-based nested case-control study using the administrative databases of Saskatchewan Health to assess the study objective. We identified cases of type 2 diabetes based on diagnostics codes and prescription records for individuals over the age of 20 years. For each case subject, two control subjects were randomly selected from the nondiabetic population during the same index year. History of depression, based on diagnostic codes and antidepressant prescription, was ascertained up to 3 years before index date. Simple and multivariate logistic regression analysis was used to estimate the odds ratio (OR) and 95% CIs, after adjusting for age, sex, and frequency of physician visits. RESULTS--Individuals with newly diagnosed diabetes (1,622 of 33,257; 4.9%) were 30% more likely to have had a previous history of depression compared with people without diabetes (2,279 of 59,420; 3.8%). This increased risk remained after controlling for sex and number of physician visits but was limited to subjects 20-50 years of age (adjusted OR 1.23 [95% CI 1.10-1.37]) and not in those aged [&ge]51 years (0.92 [0.84-1.00]). CONCLUSIONS--Depression appears to increase the risk of developing diabetes by [~]23% in younger adults. This provides information regarding the temporality of the relationship between diabetes and depression.

Brown, M. A. and J. L. Shirley (2005). "Enhancing women's mood and energy: a research-based program for subthreshold depression using light, exercise, and vitamins." Holist Nurs Pract 19(6): 278-84.

The prevalence and clinical significance of subthreshold forms of depression with sequelae comparable to major depression have been recently described in the literature; however, research on effective treatment is rare. A new intervention program that combines a specific regimen of light, exercise, and vitamins is effective in improving women's mood and overall sense of well-being. This program is well suited to many patients who present with somatic and psychological symptoms consistent with subthreshold depression.

Brown, R. P. and P. L. Gerbarg (2001). "Herbs and nutrients in the treatment of depression, anxiety, insomnia, migraine, and obesity." J Psychiatr Pract 7(2): 75-91.

Although a multitude of pharmaceutical agents are available for the treatment of mood disorders, anxiety and insomnia, many patients have difficulty tolerating the side effects, do not respond adequately, or eventually lose their response. Many therapeutic herbs and nutrients have far fewer side effects and may provide an alternative treatment or can be used to enhance the effect of prescription medications. In the article, the authors review the quality of the evidence supporting the clinical effects of a number of commonly used types of complementary/alternative medicine (CAM) for mood disorders, anxiety, and insomnia. They review data on the use of St. John's Wort, S-adenosyl-methionine (SAM-e), B vitamins, inositol, omega-3 fatty acids, and choline for mood disorders; data on the use of kava and other herbal agents and fish extract for anxiety and insomnia; and data on valerian and melatonin for insomnia. The authors also discuss the use of CAM to treat migraines, which may be comorbid with mood and anxiety disorders, and obesity, which can occur as a side effect of psychotropic medications. They consider the data on feverfew and butterbur for migraines and on chromium picolinate and the combination of ephedrine and caffeine for obesity. The authors also review issues related to comorbid medical illness, side effects, drug interactions, dosage, and brand selection.

Browne, J. C., K. M. Scott, et al. (2005). "Fish consumption in pregnancy and omega-3 status after birth are not associated with postnatal depression." J Affect Disord.

BACKGROUND: Research to date suggests a relationship between fish consumption, omega-3 polyunsaturated fatty acids, and depression. However, interpretation of this research is difficult due to methodological limitations. Postpartum women provide an excellent opportunity to examine these relationships because omega-3s are transferred from mother to fetus during pregnancy and from mother to child after birth through breast milk. Hence new mothers are more likely to be depleted in omega-3s. Our aim was to determine whether prenatal fish consumption and omega-3 status after birth were associated with postnatal depression. METHODS: Eighty first-time mothers were recruited; 41 who scored on or over the cut-off on one of two depression-screening instruments, and 39 in the control group. Depression was diagnosed using the Composite International Diagnostic Interview. Fish consumption was measured during pregnancy, and depression and omega-

3 status were determined postnatally. Logistic regression and t-tests were used to examine relationships between fish consumption, omega-3 status, and postnatal depression, while controlling for known covariates. RESULTS: Prenatal fish consumption was not predictive of postnatal depression, and postnatal omega-3 status was not associated with postnatal depression. However, prenatal fish consumption did predict omega-3 status after birth. LIMITATIONS: Prenatal fish consumption was measured using only a food frequency questionnaire, and no participants consumed oily fish (rich in omega-3s) regularly. CONCLUSIONS: There was no association between postnatal depression and either fish consumption in early pregnancy, or omega-3 status after birth. Our findings make it difficult to justify trials of omega-3 polyunsaturated fatty acids in the treatment of postnatal depression.

Cesari, M., S. B. Kritchevsky, et al. (2005). "Sarcopenia, obesity, and inflammation--results from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors study." Am J Clin Nutr 82(2): 428-434.

Background: Age-related body-composition changes are associated with health-related outcomes in elders. This relation may be explained by inflammation and hemostatic abnormalities. Objectives: Our objectives were to evaluate the relation between body-composition measures [body mass index (BMI), total fat mass, and appendicular lean mass (aLM)] and C-reactive protein (CRP), interleukin 6 (IL-6), and plasminogen activator inhibitor 1 (PAI-1) and to explore the effect of obesity and sarcopenia on CRP, IL-6, and PAI-1 concentrations. Design: The data are from the Trial of Angiotensin Converting Enzyme Inhibition and Novel Cardiovascular Risk Factors (TRAIN) study baseline visit (n = 286; mean age = 66.0 y). Total fat mass and aLM were assessed with a dual-energy X-ray absorptiometry scan. Linear regressions were performed between body-composition measures and CRP, IL-6, or PAI-1 concentrations. The effect of sarcopenia and obesity (defined as the percentage of fat mass) on CRP, IL-6, and PAI-1 concentrations was evaluated with the use of analyses of covariance. Results: CRP and IL-6 were positively associated with both BMI [{beta} = 0.027 (P = 0.03) and {beta} = 0.048 (P < 0.001), respectively] and total fat mass [{beta} = 0.049 (P < 0.001) and {beta} = 0.055 (P < 0.001), respectively] and were inversely associated with fat-adjusted aLM [{beta} = -0.629 (P = 0.002) and {beta} = -0.467 (P = 0.02), respectively]. PAI-1 was positively associated with both BMI ({beta} = 0.038, P = 0.005) and total fat mass ({beta} = 0.032, P = 0.007). No significant interaction was found between either obesity or sarcopenia and CRP, IL-6, and PAI-1 concentrations. Obesity remained significantly associated with high CRP and IL-6 concentrations after adjustments for sarcopenia. Conclusions: CRP and IL-6 are positively associated with total fat mass and negatively associated with aLM. Obesity-associated inflammation may play an important role in the age-related process that leads to sarcopenia. The relation of inflammation with sarcopenia was not independent of any of the considered obesity indexes.

Charney, D. S. and H. K. Manji (2004). "Life Stress, Genes, and Depression: Multiple Pathways Lead to Increased Risk and New Opportunities for Intervention." Sci. STKE 2004(225): re5-.

Major depression is a common, severe, chronic, and often life-threatening illness. There is a growing appreciation that, far from being a disease with purely psychological manifestations, major depression is a systemic disease with deleterious effects on multiple organ systems. Stressful life events have a substantial causal association with depression, and there is now compelling evidence that even early life stress constitutes a major risk factor for the subsequent development of depression. The emerging evidence suggests that the combination of genetics, early life stress, and ongoing stress may ultimately determine individual responsiveness to stress and the vulnerability to psychiatric disorders, such as depression. It is likely that genetic factors and life stress contribute not only to neurochemical alterations, but also to the impairments of cellular plasticity and resilience observed in depression. Recent preclinical and clinical studies have shown that signaling pathways involved in regulating cell plasticity and resilience are long-term targets for the actions of antidepressant agents. Agents capable of reversing the hypothesized impairments of cellular resilience, reductions in brain volume, and cell death or atrophy in depression have the potential of becoming new therapeutic classes of antidepressant drugs. Novel cellular targets include agents targeting neurotrophic pathways, glucocorticoid signaling, phosphodiesterase activity, and glutamatergic throughput. The future development of treatments that more directly target molecules in critical CNS (central nervous system) signaling pathways that regulate cellular plasticity thus hold promise as novel, improved long-term treatments for major depression.

Coppen, A. and C. Bolander-Gouaille (2005). "Treatment of depression: time to consider folic acid and vitamin B12." J Psychopharmacol 19(1): 59-65.

We review the findings in major depression of a low plasma and particularly red cell folate, but also of low vitamin B12 status. Both low folate and low vitamin B12 status have been found in studies of depressive patients, and an association between depression and low levels of the two vitamins is found in studies of the general population. Low plasma or serum folate has also been found in patients with recurrent mood disorders treated by lithium. A link between depression and low folate has similalrly been found in patients with alcoholism. It is interesting to note that Hong Kong and Taiwan populations with traditional Chinese diets (rich in folate), including patients with major depression, have high serum folate concentrations. However, these countries have very low life time rates of major depression. Low folate levels are furthermore linked to a poor response to antidepressants, and treatment with folic acid is shown to improve response to antidepressants. A recent study also suggests that high vitamin B12 status may be associated with better treatment outcome. Folate and vitamin B12 are major determinants of one-carbon metabolism, in which S-adenosylmethionine (SAM) is formed. SAM donates methyl groups that are crucial for neurological function. Increased plasma homocysteine is a functional marker of both folate and vitamin B12 deficiency. Increased homocysteine levels are found in depressive patients. In a large population study from Norway increased plasma homocysteine was associated with increased risk of depression but not anxiety. There is now substantial evidence of a common decrease in serum/red blood cell folate, serum vitamin B12 and an increase in plasma homocysteine in depression. Furthermore, the MTHFR C677T polymorphism that impairs the homocysteine metabolism is shown to be overrepresented among depressive patients, which strengthens the association. On the basis of current data, we suggest that oral doses of both folic acid (800 {micro}g daily) and vitamin B12 (1 mg daily) should be tried to improve treatment outcome in depression.

Dallman, M. F., N. Pecoraro, et al. (2003). "Chronic stress and obesity: A new view of "comfort food"." PNAS 100(20): 11696-11701.

The effects of adrenal corticosteroids on subsequent adrenocorticotropin secretion are complex. Acutely (within hours), glucocorticoids (GCs) directly inhibit further activity in the hypothalamo-pituitary-adrenal axis, but the chronic actions (across days) of these steroids on brain are directly excitatory. Chronically high concentrations of GCs act in three ways that are functionally congruent. (i) GCs increase the expression of corticotropin-releasing factor (CRF) mRNA in the central nucleus of the amygdala, a critical node in the emotional brain. CRF enables recruitment of a chronic stress-response network. (ii) GCs increase the salience of pleasurable or compulsive activities (ingesting sucrose, fat, and drugs, or wheel-running). This motivates ingestion of "comfort food." (iii) GCs act systemically to increase abdominal fat depots. This allows an increased signal of abdominal energy stores to inhibit catecholamines in the brainstem and CRF expression in hypothalamic neurons regulating adrenocorticotropin. Chronic stress, together with high GC concentrations, usually decreases body weight gain in rats; by contrast, in stressed or depressed humans chronic stress induces either increased comfort food intake and body weight gain or decreased intake and body weight loss. Comfort food ingestion that produces abdominal obesity, decreases CRF mRNA in the hypothalamus of rats. Depressed people who overeat have decreased cerebrospinal CRF, catecholamine concentrations, and hypothalamo-pituitary-adrenal activity. We propose that people eat comfort food in an attempt to reduce the activity in the chronic stress-response network with its attendant anxiety. These mechanisms, determined in rats, may explain some of the epidemic of obesity occurring in our society.

David, M. and F. Maurizio (2002). "Role of S-adenosyl-L-methionine in the treatment of depression: A review of the evidence." The American Journal of Clinical Nutrition 76(5): S1158.

Major depression remains difficult to treat, despite the wide array of registered antidepressants available. In recent years there has been a surge in the popularity of natural or alternative medications. Despite this growing popularity, there is limited evidence for the effectiveness of many of these natural treatments. *S*-adenosyl-L-methionine (SAMe) is one of the better studied of the natural remedies. SAMe is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. Derived from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, SAMe has been postulated to have antidepressant properties. A small number of clinical trials with parenteral or oral SAMe have shown that, at doses of 200–1600 mg/d, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAMe may have a faster onset of action than do conventional

antidepressants and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer disease. SAMe is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAMe appears to be safe and effective in the treatment of depression, but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAMe's place in the psychopharmacologic armamentarium.

Davis, J. M., N. L. Alderson, et al. (2000). "Serotonin and central nervous system fatigue: nutritional considerations." Am J Clin Nutr 72(2): 573S-578.

Fatigue from voluntary muscular effort is a complex phenomenon involving the central nervous system (CNS) and muscle. An understanding of the mechanisms within muscle that cause fatigue has led to the development of nutritional strategies to enhance performance. Until recently, little was known about CNS mechanisms of fatigue, even though the inability or unwillingness to generate and maintain central activation of muscle is the most likely explanation of fatigue for most people during normal daily activities. A possible role of nutrition in central fatigue is receiving more attention with the development of theories that provide a clue to its biological mechanisms. The focus is on the neurotransmitter serotonin [5-hydroxytryptamine (5-HT)] because of its role in depression, sensory perception, sleepiness, and mood. Nutritional strategies have been designed to alter the metabolism of brain 5-HT by affecting the availability of its amino acid precursor. Increases in brain 5-HT concentration and overall activity have been associated with increased physical and perhaps mental fatigue during endurance exercise. Carbohydrate (CHO) or branched-chain amino acid (BCAA) feedings may attenuate increases in 5-HT and improve performance. However, it is difficult to distinguish between the effects of CHO on the brain and those on the muscles themselves, and most studies involving BCAA show no performance benefits. It appears that important relations exist between brain 5-HT and central fatigue. Good theoretical rationale and data exist to support a beneficial role of CHO and BCAA on brain 5-HT and central fatigue, but the strength of evidence is presently weak.

De Vriese, S. R., A. B. Christophe, et al. (2003). "Lowered serum n-3 polyunsaturated fatty acid (PUFA) levels predict the occurrence of postpartum depression: further evidence that lowered n-PUFAs are related to major depression." Life Sci 73(25): 3181-7.

Several studies have shown that major depression is accompanied by alterations in serum fatty acid composition, e.g. reduced n-3 fatty acids and an increased 20:4n-6/20:5n-3 ratio in serum. Moreover, pregnancy leads to depletion of maternal serum 22:6n-3 and after delivery maternal serum 22:6n-3 steadily declines further. Therefore, the aim of the present study was to investigate whether the postpartum fatty acid profile of maternal serum phospholipids (PL) and cholesteryl esters (CE) differs in women who develop postpartum depression compared to controls. We compared the fatty acid composition shortly after delivery of 10 women who developed postpartum depression and 38 women who did not. After delivery, 22:6n-3 and the sum of the n-3 fatty acids in PL and CE was significantly lower in the group of mothers who developed a postpartum depression. The ratio of Sigman-6/Sigman-3 fatty acids in PL was, postpartum, significantly higher in the depressed group as compared to the controls. The abnormalities in fatty acid status previously observed in major depression are now also confirmed in postpartum depression. These results indicate that pregnant women who are at risk to develop postpartum depression may benefit from a prophylactic treatment with n-3 PUFAs, such as a combination of 20:5n-3 and 22:6n-3.

Eckhardt, R. B. (2001). "Genetic Research and Nutritional Individuality." J. Nutr. 131(2): 336S-339.

Recent genetic research builds on a base established over the last century by physicians and nutritional scientists, who introduced the concept of biochemical individuality and documented its significance for understanding a wide variety of problems in human health. Current comparative genomic investigations on a variety of organisms (Haemophilus influenzae, Saccharomyces cerevisiae, Caenorhabditis elegans, Drosophila melanogaster, Homo sapiens) have established the existence of numerous orthologs (proteins in different organisms that show significant sequence similarities over 80% of their lengths), suggesting significant conservation of structure and probably some of function as well. At the same time, molecular comparisons among individuals within our own species show the existence of abundant molecular variants, many of which have been shown to have functional significance in nutritional and related metabolic contexts. The combination of biochemical individuality and known functional utilities of allelic variants should converge to create a situation in which nutritional optima can be specified as part of comprehensive lifestyle prescriptions tailored to the needs of each person.

Ford, D. E. and T. P. Erlinger (2004). "Depression and C-Reactive Protein in US Adults: Data From the Third National Health and Nutrition Examination Survey." Arch Intern Med 164(9): 1010-1014.

Background The biological mechanisms by which depression might increase risk of cardiovascular disease are not clear. Inflammation may be a key element in the development of atherosclerotic cardiovascular disease. Our objective was to determine the association between major depression and elevated C-reactive protein (CRP) level in a nationally representative cohort. Methods We estimated the odds of elevated CRP level (>0.21 mg/mL) associated with depression in 6914 noninstitutionalized men and women (age, 18-39 years) from the Third National Health and Nutrition Examination Survey (NHANES III). Results The prevalence of lifetime major depression was 5.7% for men and 11.7% for women. The prevalence of elevated CRP level was 13.7% for men and 27.3% for women. A history of major depression was associated with elevated CRP level (odds ratio [OR], 1.64; 95% confidence interval [CI], 1.20-2.24). The association between depression and CRP was much stronger among men than among women. Results were adjusted for age, African American race, body mass index, total cholesterol, log triglycerides, diabetes, systolic blood pressure, smoking status, alcohol use, estrogen use in women, aspirin use, ibuprofen use, and self-reported health status. Compared with men without a history of depression, CRP levels were higher among men who had a more recent (within 1 year) episode of depression (adjusted OR, 3.00; 95% CI, 1.39-6.48) and who had recurrent ([IMG]=" BORDER="0">2 episodes) depression (adjusted OR, 3.55; 95% CI, 1.55-8.14). Conclusion Major depression is strongly associated with increased levels of CRP among men and could help explain the increased risk of cardiovascular disease associated with depression in men.

Fortes, C., S. Farchi, et al. (2003). "Depressive symptoms lead to impaired cellular immune response." Psychother Psychosom 72(5): 253-60.

BACKGROUND: The association between depression and immune response is not yet clear. The biological mechanisms by which depression alters the immune system is not yet understood. The purpose of this study was to investigate the longitudinal relationship between depressive symptoms and cellular immune response. METHODS: A cohort study with a baseline measurement and three annual health assessments was set up in a residential home for elderly people in Rome, Italy. A total of 166 residents aged 65 years and older, mean age 81 years, were interviewed and blood samples were collected at each annual assessment. Percentage changes in lymphocytes and T-cell subsets related to depressive symptoms were estimated over a period of 4 years, using regression models for repeated measurements. RESULTS: Elderly people with seven or more symptoms of depression, according to the Geriatric Depression Scale, had a lower percentage of CD4+DR+ T-cells over 4 years [beta = -20.2; 95% confidence interval (CI) = -33.0 to -4.9] and CD8+DR+ T-cells (beta = -26.9; 95% CI = -42.5 to -7.0) than elderly with less than seven symptoms of depression, after adjusting for confounding factors (sex, age, marital status, education, smoking habit, nutritional status, chronic diseases, disability and the use of benzodiazepines). CONCLUSION: The results of this study suggest an adverse effect of depressive symptoms on immune response. It remains to be determined whether these depression-associated immune changes are related to the onset or course of physical illness and the increased mortality observed in depressed old people.

Freeman, M. P., J. R. Hibbeln, et al. (2006). "Randomized dose-ranging pilot trial of omega-3 fatty acids for postpartum depression." Acta Psychiatr Scand 113(1): 31-5.

Objective: Postpartum depression (PPD) affects 10-15% of mothers. Omega-3 fatty acids are an intriguing potential treatment for PPD. Method: The efficacy of omega-3 fatty acids for PPD was assessed in an 8-week dose-ranging trial. Subjects were randomized to 0.5 g/day (n = 6), 1.4 g/day (n = 3), or 2.8 g/day (n = 7). Results: Across groups, pretreatment Edinburgh Postnatal Depression Scale (EPDS) and Hamilton Rating Scale for Depression (HRSD) mean scores were 18.1 and 19.1 respectively; post-treatment mean scores were 9.3 and 10.0. Percent decreases on the EPDS and HRSD were 51.5% and 48.8%, respectively; changes from baseline were significant within each group and when combining groups. Groups did not significantly differ in pre- or post-test scores, or change in scores. The treatment was well tolerated. Conclusion: This study was limited by small sample size and lack of placebo group. However, these results support further study of omega-3 fatty acids as a treatment for PPD.

Greenfield, J. R. and K. Samaras (2006). "Evaluation of pituitary function in the fatigued patient: a review of 59 cases." Eur J Endocrinol 154(1): 147-157.

Objective: The aim of this study was to review the results of dynamic pituitary testing in patients presenting with fatigue. Methods: We reviewed clinical histories and insulin tolerance test (ITT) results of 59 patients who presented with fatigue and other symptoms of glucocorticoid insufficiency over a 4-year period. All patients referred for ITT had an early-morning cortisol level of <400 nM and a low or normal ACTH level. Results: Peak cortisol and GH responses following insulin-induced hypoglycaemia were normal in only seven patients (12%). Median age of the remaining 52 patients was 47 years (range, 17-67 years); all but five were female. Common presenting symptoms were neuroglycopaenia (n = 47), depression (n = 37), arthralgia and myalgia (n = 28), weight gain (n = 25), weight loss (n = 9), postural dizziness (n = 15) and headaches (n = 13). Other medical history included autoimmune disease (n = 20; particularly Hashimoto's thyroiditis, Graves' disease and coeliac disease), postpartum (n = 8) and gastrointestinal (n = 2) haemorrhage and hyperprolactinaemia (n = 13). 31 subjects had peak cortisol levels of <500 nM (suggestive of ACTH deficiency; 18 of whom had levels < 400 nM) and a further six had indeterminate results (500-550 nM). The remaining 15 subjects had normal cortisol responses (median 654 nM; range, 553-1062 nM) but had low GH levels following hypoglycaemic stimulation (5.9 mU/l; 3-11.6 mU/l). Conclusion: Our results suggest that patients presenting with fatigue and symptoms suggestive of hypocortisolism should be considered for screening for secondary adrenal insufficiency, particularly in the presence of autoimmune disease or a history of postpartum or gastrointestinal haemorrhage. Whether physiological glucocorticoid replacement improves symptoms in this patient group is yet to be established.

Hellhammer, J., E. Fries, et al. (2004). "Effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) on the endocrine and psychological responses to mental stress." Stress 7(2): 119-26.

Phosphatidylserine, derived from cow brains, has been shown previously to dampen the ACTH and cortisol response to physical stress. Further research investigated the influence of soy lecithin phosphatidylserine supplementation on mood and heart rate when faced with an acute stressor. In this study, we investigated the effects of soy lecithin phosphatidic acid and phosphatidylserine complex (PAS) supplementation on pituitary adrenal reactivity (ACTH, cortisol) and on the psychological response (Spielberger State Anxiety Inventory stress subscale) to a mental and emotional stressor. Four groups of 20 subjects were treated for three weeks with daily dosages of either 400 mg PAS, 600 mg PAS, 800 mg PAS, or placebo before exposure to the Trier Social Stress Test (TSST). Treatment with 400 mg PAS resulted in a pronounced blunting of both serum ACTH and cortisol, and salivary cortisol responses to the TSST, but did not affect heart rate. The effect was not seen with larger doses of PAS. With regard to the psychological response, 400 mg PAS seemed to exert a specific positive effect on emotional responses to the TSST. While the placebo group showed the expected increase in distress after the test, the group treated with 400 mg PAS showed decreased distress. These data provide initial evidence for a selective stress dampening effect of PAS on the pituitary-adrenal axis, suggesting the potential of PAS in the treatment of stress related disorders.

Hintikka, J., T. Tolmunen, et al. (2003). "High vitamin B12 level and good treatment outcome may be associated in major depressive disorder." BMC Psychiatry 3: 17.

BACKGROUND: Despite of an increasing body of research the associations between vitamin B12 and folate levels and the treatment outcome in depressive disorders are still unsolved. We therefore conducted this naturalistic prospective follow-up study. Our aim was to determine whether there were any associations between the vitamin B12 and folate level and the six-month treatment outcome in patients with major depressive disorder. Because vitamin B12 and folate deficiency may result in changes in haematological indices, including mean corpuscular volume, red blood cell count and hematocrit, we also examined whether these indices were associated with the treatment outcome. METHODS: Haematological indices, erythrocyte folate and serum vitamin B12 levels were determined in 115 outpatients with DSM-III-R major depressive disorder at baseline and serum vitamin B12 level again on six-month follow-up. The 17-item Hamilton Depression Rating Scale was also compiled, respectively. In the statistical analysis we used chi-squared test, Pearson's correlation coefficient, the Student's t-test, analysis of variance (ANOVA), and univariate and multivariate linear regression analysis. RESULTS: Higher vitamin B12 levels significantly associated with a better outcome. The association between the folate level and treatment outcome was weak and probably not independent. No relationship was found between haematological indices and the six-month outcome.

CONCLUSION: The vitamin B12 level and the probability of recovery from major depression may be positively associated. Nevertheless, further studies are suggested to confirm this finding.

Hoffer, L. J. (2001). "Clinical nutrition: 1. Protein-energy malnutrition in the inpatient." CMAJ 165(10): 1345-1349.

PEM is caused by starvation. It is the disease that develops when protein intake or energy intake, or both, chronically fail to meet the body's requirements for these nutrients. PEM has always been a common disease, and humans have adaptive mechanisms for slowing and, in most cases, arresting its progress. Fat loss is slowed by a reduction in energy expenditure that the body accomplishes both by reducing the metabolic rate per unit of the metabolically active tissues and by jettisoning some of the body's lean tissue (protein) store. Such a protein-depleted body also requires less dietary protein. Muscle protein, which normally accounts for about 80% of the lean tissue mass, bears the brunt of the loss, whereas the "central" lean tissues (liver, gastrointestinal tract, kidneys, blood and immune cells) are relatively spared. As long as the starvation ration of energy and protein is not too low, successful adaptation will reduce energy and protein requirements to match it, restoring homeostasis and maintaining key physiologic functions. The physiologic cost of this adaptation is a lowered metabolic rate and reduced muscle mass (including reduced cardiac and respiratory muscle mass); its clinical consequences include muscular weakness and functional disability, reduced cardiac and respiratory capacity, mild hypothermia and a reduced body protein reserve.

Hu, F. B. (2005). "Protein, body weight, and cardiovascular health." Am J Clin Nutr 82(1): 242S-247.

Widespread popularity of high-protein diets has drawn controversy as well as scientific interest. By reducing intake of carbohydrates and increasing consumption of fats and proteins, such diets are thought to increase satiety, facilitate weight loss, and improve cardiovascular risk factors. In recent years, many randomized controlled studies have compared the effects of higher-protein diets on weight loss and cardiovascular risk factors with those of lower-protein diets. The aim of this review was to provide an overview of experimental and epidemiologic evidence regarding the role of protein in weight loss and cardiovascular risk. Emerging evidence from clinical trials indicates that higher-protein diets increase short-term weight loss and improve blood lipids, but long-term data are lacking. Findings from epidemiologic studies show a significant relationship between increased protein intake and lower risk of hypertension and coronary heart disease. However, different sources of protein appear to have different effects on cardiovascular disease. Although optimal amounts and sources of protein cannot be determined at this time, evidence suggests a potential benefit of partially replace refined carbohydrates with protein sources low in saturated fats.

Hunt, J. R. and J. G. Penland (1999). "Iron status and depression in premenopausal women: an MMPI study. Minnesota Multiphasic Personality Inventory." Behav Med 25(2): 62-8.

To test the hypothesis that low iron status or other nutritional deficiencies are associated with symptoms of depression in premenopausal women, the authors related blood indices of iron status to scores on the Minnesota Multiphasic Personality Inventory (MMPI) and responses to a mood adjective checklist. Participants recruited locally provided fasting blood samples and completed the MMPI during the follicular phase of the menstrual cycle. Of 365 apparently healthy participants, 4% had hemoglobin < 120 g/L, 6% had transferrin saturation < 16%, 20% had ferritin < 12 micrograms/L, and 8% had clinically elevated scores (T > or = 70) on the Depression scale of the MMPI. The frequency of elevated MMPI Depression scores was unrelated to the frequency of low hemoglobin, transferrin saturation, or ferritin. The results do not support the hypothesis that low iron status contributes to symptoms of depression in women.

Hvas, A. M., S. Juul, et al. (2004). "Vitamin B6 level is associated with symptoms of depression." Psychother Psychosom 73(6): 340-3.

BACKGROUND: A low level of vitamin B6 might theoretically cause depression as vitamin B6 is a cofactor in the tryptophan-serotonin pathway. In the present study, we examined the association between depression and the phosphate derivative of vitamin B6 in plasma, pyridoxal phosphate (PLP). METHODS: In 140 individuals, symptoms of depression were evaluated by the Major Depression Inventory, and biochemical markers of vitamin B deficiency were measured. RESULTS: We found that 18 (13%) individuals were depressed. A low plasma level of PLP was significantly associated with the depression score

(p=0.002). No significant association was found between depression and plasma vitamin B12 (p=0.13), plasma methylmalonic acid (p=0.67), erythrocyte folate (p=0.77), and plasma total homocysteine (p=0.16). CONCLUSION: Our study suggests that a low level of plasma PLP is associated with symptoms of depression. Randomized trials are now justified and needed in order to examine whether treatment with vitamin B6 may improve symptoms of depression.

Hvas, A. M., S. Juul, et al. (2004). "No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study." J Affect Disord 81(3): 269-73.

BACKGROUND: Associations between vitamin B-12 deficiency and impaired cognitive function and depression have been reported. METHODS: A randomized placebo controlled study including 140 individuals with an increased plasma methylmalonic acid (0.40-2.00 micromol/l) not previously treated with vitamin B-12. Cognitive function was assessed by the Cambridge Cognitive Examination (CAMCOG), Mini-Mental State Examination (MMSE), and a 12-words learning test. Symptoms of depression were evaluated by the Major Depression Inventory. The main outcome measure was change in cognitive function and depression score from baseline to follow-up 3 months later. RESULTS: At baseline 78 (56%) individuals had cognitive impairment judged from the CAMCOG score and 40 (29%) according to the MMSE; 18 (13%) individuals had symptoms of depression. No improvement was found in cognitive function comparing the treatment and placebo group (total CAMCOG score: P = 0.43), nor among individuals with only slightly impaired cognitive function (n = 44, total CAMCOG score: P = 0.42). The treatment group did not improve in depression score as compared to the placebo group (P = 0.18). LIMITATIONS: The duration of impaired cognitive function was unknown. CONCLUSIONS: A high proportion of individuals with an increased plasma methylmalonic acid had impaired cognitive function, and a rather high prevalence of depression was observed. However, vitamin B-12 treatment did not improve cognitive function or symptoms of depression within the 3-months study period.

Irmisch, G., D. Schlafke, et al. (2006). "Relationships between fatty acids and psychophysiological parameters in depressive inpatients under experimentally induced stress." Prostaglandins Leukot Essent Fatty Acids 74(2): 149-56.

Fatty acids can influence important cellular and hormonal processes in the human body. Non-adequate contents of fatty acids, e.g., in blood, can cause and/or result in various diseases. In depressive patients, changes in fatty acid concentrations were found (deficits in omega3-fatty acids, in particular). This paper poses the question whether there are any relations between psychophysiological parameters and changes in fatty acid compositions. The concentration of fatty acids in serum of 118 psychiatric inpatients measured directly before and after experimentally induced stress of about 1h were analysed in relation to psychophysiological parameters continuously registered during the experimental sessions at admission, discharge and at 3 months follow-up. Systolic and diastolic blood pressure, finger pulse amplitude, forehead temperature (FD) and the EMG activity of the musculus zygomaticus consistently correlated with concentrations of single unsaturated oleic (18:1n-9) and erucic acid (22:1) and saturated myristic (14:0) and lauric acid (12:0). Negative relations were found between FD and the concentration of arachidonic acid (20:4n-6) as well as of palmitoleic acid (16:1). Furthermore, the higher the concentration of the erucic acid at discharge the higher the depression score as assessed by the Beck depression inventory (BDI). High concentrations of palmitoleic acid and lauric acid were related to a low level of depression (BDI and Hamilton scores). The implications of these findings for add-on treatment regimens in depression are discussed.

Kahl, K. G., S. Rudolf, et al. (2005). "Bone Mineral Density, Markers of Bone Turnover, and Cytokines in Young Women With Borderline Personality Disorder With and Without Comorbid Major Depressive Disorder." Am J Psychiatry 162(1): 168-174.

OBJECTIVE: The pathogenesis of bone loss in major depressive disorder is a matter of debate. Studies of bone loss in nonpsychiatric medical disorders have found an association between the activation of osteoclastic cells and an imbalance of pro- and antiinflammatory cytokines. Since major depressive disorder is also associated with alterations in serum cytokine concentrations, the authors hypothesized that bone loss in patients with major depressive disorder and comorbid borderline personality disorder may be associated with cytokines capable of activating osteoclastic cells. METHOD: Twenty-two patients with borderline personality disorder and comorbid current or lifetime major depressive disorder were compared with 16 patients with borderline personality disorder who did not have major depressive disorder and 20 healthy volunteers. Bone

mineral density was assessed by means of dual-energy x-ray absorptiometry. Markers of bone turnover as well as endocrine and immune measures were determined. RESULTS: The bone mineral density of 10 patients with borderline disorder plus current major depressive episode was significantly lower than that of the healthy subjects and the patients with borderline personality disorder without depression. Values of crosslaps, osteocalcin, serum cortisol, tumor necrosis factor-{alpha} (TNF-{alpha}), and interleukin-6 were significantly higher in the patients with borderline disorder plus current major depressive episode than in the healthy subjects. Crosslaps correlated positively with TNF-{alpha} but negatively with bone mineral density at the lumbar spine. Patients with borderline personality disorder who did not have current or lifetime depression displayed no alterations of either bone mineral density or the immunological and hormonal measures examined. CONCLUSIONS: Young women with comorbid borderline personality disorder and major depressive disorder have an elevated risk for osteoporosis. Borderline personality disorder per se is not associated with low bone mineral density. These data suggest that the immune and endocrine disturbances associated with depressive disorders in the context of borderline personality disorder may play a role in the pathophysiological process underlying bone loss in the patients studied.

Kaput, J. and R. L. Rodriguez (2004). "Nutritional genomics: the next frontier in the postgenomic era." Physiol. Genomics 16(2): 166-177.

The interface between the nutritional environment and cellular/genetic processes is being referred to as "nutrigenomics." Nutrigenomics seeks to provide a molecular genetic understanding for how common dietary chemicals (i.e., nutrition) affect health by altering the expression and/or structure of an individual's genetic makeup. The fundamental concepts of the field are that the progression from a healthy phenotype to a chronic disease phenotype must occur by changes in gene expression or by differences in activities of proteins and enzymes and that dietary chemicals directly or indirectly regulate the expression of genomic information. We present a conceptual basis and specific examples for this new branch of genomic research that focuses on the tenets of nutritional genomics: 1) common dietary chemicals act on the human genome, either directly or indirectly, to alter gene expression or structure; 2) under certain circumstances and in some individuals, diet can be a serious risk factor for a number of diseases; 3) some diet-regulated genes (and their normal, common variants) are likely to play a role in the onset, incidence, progression, and/or severity of chronic diseases; 4) the degree to which diet influences the balance between healthy and disease states may depend on an individual's genetic makeup; and 5) dietary intervention based on knowledge of nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used to prevent, mitigate, or cure chronic disease.

Kinder, L. S., M. R. Carnethon, et al. (2004). "Depression and the Metabolic Syndrome in Young Adults: Findings From the Third National Health and Nutrition Examination Survey." Psychosom Med 66(3): 316-322.

OBJECTIVE: Previous reports have suggested that depression may lead to the development of cardiovascular disease through its association with the metabolic syndrome; however, little is known about the relationship between depression and the metabolic syndrome. The aim of this study was to establish an association between depression and the metabolic syndrome in a nationally representative sample. METHODS: The Third National Health and Nutrition Examination Survey is a population-based health survey of noninstitutionalized US citizens completed between 1988 and 1994. Three thousand one hundred eighty-six men and 3003 women, age 17 to 39, free of coronary heart disease and diabetes, completed the depression module from the Diagnostic Interview Schedule and a medical examination that provided clinical data needed to establish the presence of the metabolic syndrome, as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Cholesterol in Adults. RESULTS: Women with a history of a major depressive episode were twice as likely to have the metabolic syndrome compared with those with no history of depression. The relationship between depression and metabolic syndrome remained after controlling for age, race, education, smoking, physical inactivity, carbohydrate consumption, and alcohol use. Men with a history of depression were not significantly more likely to have the metabolic syndrome. CONCLUSIONS: The prevalence of the metabolic syndrome is elevated among women with a history of depression. It is important to better understand the role depression may play in the effort to reduce the prevalence of the metabolic syndrome and its health consequences.

Kotler, D. P. (2000). "Cachexia." Ann Intern Med 133(8): 622-634.

Cachexia represents the clinical consequence of a chronic, systemic inflammatory response, and its manifestations differ considerably from those of starvation. Although cachexia is classically associated with chronic infections and malignant conditions, some of its elements have been identified in a wide variety of chronic diseases and in aging persons. Cachexia has repeatedly been associated with adverse clinical outcomes. The changes seen in cachexia are multidimensional and highly coordinated. Most obvious is a redistribution of the body's protein content, with preferential depletion of skeletal muscle and an increase in the synthesis of proteins involved in the response to tissue injury--the so-called acute-phase response. The physiologic, metabolic, and behavioral changes of cachexia are tightly regulated by cytokines, which signal the synthesis of acute-phase proteins as well as changes in intermediary metabolism that provide substrate and energy. The metabolic adaptations, notably the increase in the rate of protein degradation, limit the ability of hypercaloric feeding to reverse the depletion of lean mass. Recent studies have demonstrated the ability of anabolic and anticatabolic agents to mitigate the loss of skeletal muscle and to improve clinical outcomes in selected circumstances. Preclinical initiatives target the cytokine regulation of protein metabolism. It should be stressed that metabolic manipulation in cachexia could have positive or negative clinical effects, which must be distinguished through appropriate clinical trials.

Ledochowski, M., B. Widner, et al. (2000). "Carbohydrate malabsorption syndromes and early signs of mental depression in females." Dig Dis Sci 45(7): 1255-9.

Fructose and lactose malabsorption are characterized by impaired duodenal fructose transport or by the deficiency of mucosal lactase, respectively. As a consequence, the nonabsorbed saccharides reach the colon, where they are broken down by bacteria to short fatty acids, C02, and H2. Bloating, cramps, osmotic diarrhea, and other symptoms of irritable bowel syndrome are the consequence and can be seen in about 50% of carbohydrate malabsorbers. We have previously shown that fructose as well as lactose malabsorption were associated with signs of mental depression. It was therefore of interest to investigate possible interactions between fructose and lactose malabsorption and their influence on the development of signs of depression. In all, 111 otherwise healthy volunteers (81 females and 30 males) with gastrointestinal complaints were analyzed by measuring breath H2 concentrations after an oral dose of 50 g lactose and of 50 g fructose one week apart. They were classified as normals, isolated fructose malabsorbers, isolated lactose malabsorbers, and combined fructose/lactose malabsorbers. All patients filled out a Beck's depression inventory-questionnaire. Twenty-five individuals (22.5%) were neither fructose nor lactose malabsorbers (group 1), 69 (62.2%) were only fructose malabsorbers (group 2), 4 (3.6%) were only lactose malabsorbers (group 3), and 13 (11.7%) presented with fructose and lactose malabsorption together (group 4). Isolated fructose malabsorption and combined fructose/lactose malabsorption was significantly associated with a higher Beck's depression score. Further analysis of the data show that this association was strong in females ($P < 0.01$), but there was no such association between carbohydrate malabsorption and early signs of depression in males. In conclusion, the data confirm that fructose malabsorption may play a role in the development of mental depression in females and additional lactose malabsorption seems to further increase the risk for development of mental depression.

Lee, C.-Y. J. and W. Fan (2000). "Vitamin E Supplementation Improves Cell-Mediated Immunity and Oxidative Stress of Asian Men and Women." J. Nutr. 130(12): 2932-2937.

Vitamin E is an efficient antioxidant and a modulator of the immune system. Although racial differences in both baseline vitamin E level and immunologic subsets are known, no reliable data exist for the Asian population. Furthermore, the extent of the effect of {alpha}-tocopherol in protecting lymphocyte cells against oxidative stress and its association with cell-mediated immunity have not been elucidated. This study was undertaken to investigate the immunologic and antioxidant effects of vitamin E in healthy ethnic Chinese men and women. Volunteers < 35 y old ($n = 26$) were supplemented with 233 mg/d dl-{alpha}-tocopherol for 28 d. The in vitro proliferative response to phytohemagglutinin (PHA) or lipopolysaccharide (LPS) of T-lymphocytes was determined in the study group before and after vitamin E supplementation. Cell-mediated immunity subsets and hydrogen peroxide production in T-lymphocytes were investigated by flow cytometry. The oxidant-antioxidant balance in plasma and urine was studied by spectrophotometric and gas chromatography-mass selective detection methods. The antioxidant properties of vitamin E were established ($P < 0.01$) by the elevation of plasma vitamin E, together with depression in both plasma malondialdehyde and urinary DNA adduct 8-hydroxy-2'-deoxyguanosine after supplementation. Our data suggest a specific requirement for vitamin E in total-T and T-helper cell proliferation. We present

the first evidence of the beneficial effects of supplemental vitamin E in healthy Chinese individuals on cell-mediated immunity and oxidative stress.

Lee, E. S., Y. H. Kim, et al. (2005). "Depressive Mood and Abdominal Fat Distribution in Overweight Premenopausal Women." Obes Res 13(2): 320-325.

Objective: There is increasing evidence that depressive mood is associated with central obesity, but little is known about the association between depression and abdominal fat distribution. This study investigated this relationship in premenopausal women. Research Methods and Procedures: We recruited 101 overweight premenopausal women who had no eating disorders as defined using the DSM IV criteria. Depressive mood was assessed using Zung's Self-Rating Depression Scale (SDS). Areas of visceral (VAT) and subcutaneous (SAT) adipose tissue at the level of vertebral body L4-L5 were measured using computed tomography. Associations of VAT, SAT, and the ratio of VAT to SAT with natural logarithmic transformation [(ln)]SDS were evaluated using linear regression. Anthropometric indices and physical fitness were also measured. Information on socioeconomic status, education level, and alcohol and smoking habits was obtained using self-administered questionnaires. A hospital nutritionist assessed nutritional status. All of these factors were adjusted for as possible confounding factors in the analyses. Results: The (ln)SDS score showed a positive association with the area of VAT, even after adjusting for the confounders mentioned above ($p < 0.01$). BMI, waist circumference, maximal oxygen uptake, and age were also associated with the area of VAT (all $p < 0.05$). In contrast, the (ln)SDS score was not associated with SAT ($p > 0.10$). Discussion: We showed that depressive mood is associated with VAT, not with SAT, in overweight premenopausal women. These findings may explain some of the association between depression and coronary heart disease. More studies are needed to elucidate the causal relationship.

Logan, A. C. (2004). "Omega-3 fatty acids and major depression: a primer for the mental health professional." Lipids Health Dis 3: 25.

Omega-3 fatty acids play a critical role in the development and function of the central nervous system. Emerging research is establishing an association between omega-3 fatty acids (alpha-linolenic, eicosapentaenoic, docosahexaenoic) and major depressive disorder. Evidence from epidemiological, laboratory and clinical studies suggest that dietary lipids and other associated nutritional factors may influence vulnerability and outcome in depressive disorders. Research in this area is growing at a rapid pace. The goal of this report is to integrate various branches of research in order to update mental health professionals.

Logan, A. C. and M. Katzman (2005). "Major depressive disorder: probiotics may be an adjuvant therapy." Med Hypotheses 64(3): 533-8.

Major depressive disorder (MDD) is an extremely complex and heterogeneous condition. Emerging research suggests that nutritional influences on MDD are currently underestimated. MDD patients have been shown to have elevated levels of pro-inflammatory cytokines, increased oxidative stress, altered gastrointestinal (GI) function, and lowered micronutrient and omega-3 fatty acid status. Small intestinal bacterial overgrowth (SIBO) is likely contributing to the limited nutrient absorption in MDD. Stress, a significant factor in MDD, is known to alter GI microflora, lowering levels of lactobacilli and bifidobacterium. Research suggests that bacteria in the GI tract can communicate with the central nervous system, even in the absence of an immune response. Probiotics have the potential to lower systemic inflammatory cytokines, decrease oxidative stress, improve nutritional status, and correct SIBO. The effect of probiotics on systemic inflammatory cytokines and oxidative stress may ultimately lead to increased brain derived neurotrophic factor (BDNF). It is our contention that probiotics may be an adjuvant to standard care in MDD.

Maes, M., N. De Vos, et al. (2000). "Lower serum vitamin E concentrations in major depression. Another marker of lowered antioxidant defenses in that illness." J Affect Disord 58(3): 241-6.

OBJECTIVE: Major depression is associated with defective antioxidant defenses. Vitamin E is the major fat soluble antioxidant in the body. The aim of the present study is to examine serum vitamin E concentrations in major depressed patients versus normal volunteers. METHOD: Serum vitamin E concentrations were measured in 26 healthy volunteers and 42 major depressed patients by means of HPLC. Since vitamin E is a fat soluble vitamin, and serum vitamin E concentrations are

strongly related to these of low-density-lipoprotein cholesterol (LDL-C) and triglycerides, we have adjusted the results for possible differences in these lipids. The numbers of peripheral blood leukocytes were measured. RESULTS: Patients with major depression had significantly lower serum vitamin E concentrations than healthy controls. The area under the ROC (receiver operating characteristics) curve was 83%. There were significant and negative correlations between serum vitamin E and number of total leukocytes and neutrophils. CONCLUSIONS: Major depression is accompanied by significantly lower serum vitamin E concentrations, suggesting lower antioxidant defenses against lipid peroxidation. The results could, in part, explain previous findings, which suggest increased lipid peroxidation in major depression.

Marangell, L. B., J. M. Martinez, et al. (2003). "A Double-Blind, Placebo-Controlled Study of the Omega-3 Fatty Acid Docosahexaenoic Acid in the Treatment of Major Depression." Am J Psychiatry 160(5): 996-998.
OBJECTIVE: This study was an evaluation of the omega-3 fatty acid docosahexaenoic acid (DHA) for the treatment of major depression. METHOD: Thirty-six depressed patients were randomly assigned to receive DHA, 2 g/day, or placebo for 6 weeks. Response was defined a priori as a [>=]50% reduction in the score on the Montgomery-Asberg Depression Rating Scale. Thirty-five participants were evaluable; 18 received DHA, and 17 received placebo. RESULTS: Response rates were 27.8% in the DHA group and 23.5% in the placebo group. The difference in response rates between groups did not reach statistical significance. CONCLUSIONS: This trial failed to show a significant effect of DHA monotherapy in subjects with major depression.

Michelson, D. and P. W. Gold (1998). "Pathophysiologic and Somatic Investigations of Hypothalamic-Pituitary-Adrenal Axis Activation in Patients with Depression." Ann NY Acad Sci 840(1): 717-722.
Preclinical studies of inflammatory and autoimmune illnesses have demonstrated the importance of central components of the HPA axis in disease pathophysiology. The implications of these data for human illness are poorly understood. We have studied the pathophysiology of the hypercortisolism seen in two human illnesses involving the central nervous system, multiple sclerosis (MS) and depression, and looked for demonstrable somatic changes that may be associated with such hypercortisolism. Data from a study of medication-free patients with multiple sclerosis not in acute exacerbation suggest that compared with depression, MS is associated with increased prominence of hypothalamic vasopressin secretion ($p < 0.05$). Data from studies of depressed patients with mild to moderate hypercortisolism (assessed by 24-hour urinary free cortisol excretion) demonstrate marked reductions in bone mineral density compared to healthy, carefully matched controls ($p < 0.001$), as well as changes in markers of bone metabolic activity similar to those seen in patients with Cushing's disease or exogenous glucocorticoid treatment ($p < 0.05$). Taken together, these studies suggest HPA axis dysregulations demonstrated in preclinical models of autoimmune and inflammatory illness also occur in human illness and may have important and lasting somatic sequelae.

Michelson, D., C. Stratakis, et al. (1996). "Bone Mineral Density in Women with Depression." N Engl J Med 335(16): 1176-1181.
Background Depression is associated with alterations in behavior and neuroendocrine systems that are risk factors for decreased bone mineral density. This study was undertaken to determine whether women with past or current major depression have demonstrable decreases in bone density. Methods We measured bone mineral density at the hip, spine, and radius in 24 women with past or current major depression and 24 normal women matched for age, body-mass index, menopausal status, and race, using dual-energy x-ray absorptiometry. We also evaluated cortisol and growth hormone secretion, bone metabolism, and vitamin D-receptor alleles. Results As compared with the normal women, the mean ({+/-}SD) bone density in the women with past or current depression was 6.5 percent lower at the spine (1.00 {+/-} 0.15 vs. 1.07 {+/-} 0.09 g per square centimeter, $P = 0.02$), 13.6 percent lower at the femoral neck (0.76 {+/-} 0.11 vs. 0.88 {+/-} 0.11 g per square centimeter, $P<0.001$), 13.6 percent lower at Ward's triangle (0.70 {+/-}0.14 vs. 0.81 {+/-}0.13 g per square centimeter, $P<0.001$), and 10.8 percent lower at the trochanter (0.66 {+/-} 0.11 vs. 0.74 {+/-} 0.08 g per square centimeter, $P<0.001$). In addition, women with past or current depression had higher urinary cortisol excretion (71 {+/-} 29 vs. 51 {+/-} 19 {micro}g per day [196 {+/-} 80 vs. 141 {+/-} 52 nmol per day], $P = 0.006$), lower serum osteocalcin concentrations ($P = 0.04$), and lower urinary excretion of deoxypyridinoline ($P = 0.02$). Conclusions Past or current depression in women is associated with decreased bone mineral density.

Miller, G. E., N. Rohleder, et al. (2005). "Clinical Depression and Regulation of the Inflammatory Response During Acute Stress." Psychosom Med 67(5): 679-687.
Objective: This study examined whether clinical depression is associated with a differential inflammatory response to an acute bout of psychological stress. Methods: A total of 72 women participated in the study; half met diagnostic criteria for clinical depression; the others had no history of psychiatric illness. The groups were matched with respect to age and ethnicity. All subjects were exposed to a 17-minute mock-job interview; blood was drawn to assess secretion and regulation of inflammatory molecules. Results: The stressor was associated with feelings of shame and anxiety, a mobilization of monocytes, neutrophils, and C-reactive protein into the circulation, and greater endotoxin-stimulated production of interluekin-6 and tumor necrosis factor-{alpha} by white blood cells in vitro. Depressed subjects began the session with greater sensitivity to the antiinflammatory properties of glucocorticoids than control subjects. Following exposure to the stressor protocol, however, sensitivity decreased among depressed subjects and increased among controls. This was manifest by disparities in interluekin-6 and tumor necrosis factor-{alpha} production in the presence of dexamethasone. Conclusions: These findings suggest that under acutely challenging conditions, depression is associated with greater resistance to molecules that normally terminate the inflammatory cascade. An impaired capacity to regulate inflammation could underlie some of the excess morbidity and mortality that has been associated with depression.

Milner, J. A. (2004). "Molecular Targets for Bioactive Food Components." J. Nutr. 134(9): 2492S-2498.
Mounting evidence points to dietary habits as an important determinant of cancer risk and tumor behavior. Although the linkages with diet are intriguing, the literature is also laden with inconsistencies. The reasons for these inconsistencies are likely multi-factorial, but probably reflect variations in the ability of bioactive constituents to reach or affect critical molecular targets. Fluctuations in the foods consumed not only influence the intake of particular bioactive components, but may alter metabolism and potentially influence the sites of action of both essential and nonessential nutrients. Genetic polymorphisms are increasingly recognized as another factor that can alter the response to dietary components (nutritional transcriptomic effect) by influencing the absorption, metabolism, or sites of action. Likewise, variation in DNA methylation patterns and other epigenetic events that influence overall gene expression can be influenced by dietary intakes. Furthermore, variation in the ability of food components to increase or depress gene expression (nutrigenomic effect) may account for some of the observed inconsistencies in the response to dietary change. Because a host of food components are recognized to influence phosphorylation and other posttranslational events, it is also likely that these and other proteomic modifications account for at least part of the response and variation that is reported in the literature. Collectively, it is clear that bioactive food components can influence a number of key molecular events that are involved in health and disease resistance. As the era of molecular nutrition unfolds, a greater understanding of how these foods and components influence cancer will surely arise. Such information will be critical in the development of effective tailored strategies for reducing cancer burden. Just as important, however, is that as this information unfolds it is utilized within a responsible bioethical framework.

Mischoulon, D. and M. Fava (2002). "Role of S-adenosyl-L-methionine in the treatment of depression: a review of the evidence." Am J Clin Nutr 76(5): 1158S-1161.
Major depression remains difficult to treat, despite the wide array of registered antidepressants available. In recent years there has been a surge in the popularity of natural or alternative medications. Despite this growing popularity, there is limited evidence for the effectiveness of many of these natural treatments. S-adenosyl-L-methionine (SAMe) is one of the better studied of the natural remedies. SAMe is a methyl donor and is involved in the synthesis of various neurotransmitters in the brain. Derived from the amino acid L-methionine through a metabolic pathway called the one-carbon cycle, SAMe has been postulated to have antidepressant properties. A small number of clinical trials with parenteral or oral SAMe have shown that, at doses of 200-1600 mg/d, SAMe is superior to placebo and is as effective as tricyclic antidepressants in alleviating depression, although some individuals may require higher doses. SAMe may have a faster onset of action than do conventional antidepressants and may potentiate the effect of tricyclic antidepressants. SAMe may also protect against the deleterious effects of Alzheimer disease. SAMe is well tolerated and relatively free of adverse effects, although some cases of mania have been reported in bipolar patients. Overall, SAMe appears to be safe and effective in the treatment of depression,

but more research is needed to determine optimal doses. Head-to-head comparisons with newer antidepressants should help to clarify SAMe's place in the psychopharmacologic armamentarium.

Mitani, H., Y. Shirayama, et al. (2006). "Plasma levels of homovanillic acid, 5-hydroxyindoleacetic acid and cortisol, and serotonin turnover in depressed patients." Prog Neuropsychopharmacol Biol Psychiatry.
Plasma levels of ACTH, cortisol and monoamines were examined in 23 depressed patients and 31 healthy subjects. Patients showed increased plasma cortisol levels, but not plasma adrenocorticotropic hormone (ACTH) levels. The plasma levels of a dopamine metabolite, homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), were significantly decreased in the patients. In contrast, the plasma levels of a serotonin (5-HT) metabolite, hydroxyindoleacetic acid (5-HIAA), and 5-HT turnover (5-HIAA/5-HT) were increased in the depressed patients. Therefore, plasma levels of HVA and 5-HIAA are proven to be dissociable. Furthermore, plasma levels of 5-HIAA and L-DOPA have positive relationships with severity of depression. On the basis of this and the previous studies, we speculate that an increase in the plasma 5-HIAA levels might be a compensatory mechanism for stress, whereas 5-HT turnover might reflect depressive state. Taken together, plasma levels of HVA and 5-HIAA, and 5-HT turnover (5-HIAA/5-HT) could be good markers for evaluating depression.

Morris, M. S., M. Fava, et al. (2003). "Depression and folate status in the US Population." Psychother Psychosom 72(2): 80-7.
BACKGROUND: Folate deficiency and low folate status have been linked in clinic studies to depression, persistent depressive symptoms, and poor antidepressant response. These relationships have not been demonstrated in general populations. This study examined associations between depression and folate status indicators in an ethnically diverse general US population sample aged 15-39 years. METHODS: Healthy subjects whose red blood cell (RBC) folate concentrations had been measured were determined to have no depression (n = 2,526), major depression (n = 301), or dysthymia (n = 121) using a diagnostic interview schedule. Serum concentrations of folate and total homocysteine (tHcy) were also measured. RESULTS: After adjustment for sociodemographic factors, serum vitamin B(12) concentration, alcohol consumption over the past year and current status as to overweight and use of vitamin/mineral supplements, cigarettes and illegal drugs, subjects who met criteria for a lifetime diagnosis of major depression had folate concentrations in serum and RBCs that were lower than those of subjects who had never been depressed. Subjects who met criteria for dysthymia alone had lower RBC folate concentrations than never-depressed subjects, but the serum folate concentrations of the two groups were comparable. Serum tHcy concentration was not related to lifetime depression diagnoses. Low folate status was found to be most characteristic of recently recovered subjects, and a large proportion of such subjects were folate deficient. CONCLUSIONS: Low folate status was detectable in depressed members of the general US population. Folate supplementation may be indicated during the year following a depressive episode.

Murck, H., C. Song, et al. (2004). "Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression." Int J Neuropsychopharmacol 7(3): 341-9.
Preliminary evidence shows that ethyl-eicosapentaenoate (E-EPA) has a marked clinical effect when used as an adjunct in therapy-refractory depression. EPA belongs to the class of polyunsaturated omega-3 fatty acids. The mechanism of its action in depression is not fully understood. There are two related fields where the pathophysiology of refractory depression meets the effect of EPA. First, a general immunosuppressive effect of EPA meets a general immunoactivation in severe depression, especially an increase in CD4/CD8 ratio, neutrophilia, and an increase in interleukins (IL)-6 and IL-12 and of prostaglandin E2 (PGE2). Secondly, a resistance to dexamethasone (Dex) suppression of the HPA axis meets the effects of EPA on multidrug resistance reversing and HPA axis suppression. The effects of EPA on the immune system, the HPA axis, and multidrug resistance are connected through the action of a transport protein called p-glycoprotein (p-gp). Physiological and synthetic steroids such as cortisol and Dex are substrates of p-gp, and so Dex resistance in depression may be related to dysfunction of this protein. In addition, expression of p-gp is induced by PGE2, and EPA inhibits the synthesis of PGE2. The reversal of drug resistance by EPA may be mediated via this immunological mechanism and lead to its antidepressive efficacy. In addition, antidepressants such as amitriptyline, which have special efficacy in severe depression, decrease p-gp function. EPA may, furthermore, enhance the action of antidepressants, like many SSRIs that are p-gp substrates, which are actively transported out of the intracerebral space at the level of the blood-brain barrier.

Mutch, D. M., W. Wahli, et al. (2005). "Nutrigenomics and nutrigenetics: the emerging faces of nutrition." FASEB J. 19(12): 1602-1616.

The recognition that nutrients have the ability to interact and modulate molecular mechanisms underlying an organism's physiological functions has prompted a revolution in the field of nutrition. Performing population-scaled epidemiological studies in the absence of genetic knowledge may result in erroneous scientific conclusions and misinformed nutritional recommendations. To circumvent such issues and more comprehensively probe the relationship between genes and diet, the field of nutrition has begun to capitalize on both the technologies and supporting analytical software brought forth in the post-genomic era. The creation of nutrigenomics and nutrigenetics, two fields with distinct approaches to elucidate the interaction between diet and genes but with a common ultimate goal to optimize health through the personalization of diet, provide powerful approaches to unravel the complex relationship between nutritional molecules, genetic polymorphisms, and the biological system as a whole. Reluctance to embrace these new fields exists primarily due to the fear that producing overwhelming quantities of biological data within the confines of a single study will submerge the original query; however, the current review aims to position nutrigenomics and nutrigenetics as the emerging faces of nutrition that, when considered with more classical approaches, will provide the necessary stepping stones to achieve the ambitious goal of optimizing an individual's health via nutritional intervention.

Owen, A. J., M. J. Batterham, et al. (2005). "Low plasma vitamin E levels in major depression: diet or disease?" Eur J Clin Nutr 59(2): 304-6.

OBJECTIVE: Levels of vitamin E have been reported to be lower in patients suffering major depression, but whether this is due to inadequate dietary intake or the pathophysiology of depression is not known, and was the subject of the present study. SETTING: Wollongong, Australia. METHODS: Plasma vitamin E (alpha-tocopherol) was measured in 49 adults with major depression, age (mean+/-s.d.): 47+/-12 y. In a subset (n=19) usual dietary intake of vitamin E was determined by diet history. RESULTS: Subjects had significantly lower plasma alpha-tocopherol (4.71+/-0.13 mumol/mmol cholesterol) than has previously been reported for healthy Australians, and plasma alpha-tocopherol was inversely related to depression score (by Beck Depression Inventory) ($r=-0.367$, $P<0.009$). Diet analysis indicated that 89% of subjects met or exceeded the recommended intake for vitamin E, and dietary intake was not related to plasma alpha-tocopherol level in this subset. CONCLUSION: These findings suggest that plasma levels of alpha-tocopherol are lower in depression, but this is not likely to be the result of inability to meet recommended dietary intake.

Papakostas, G. I., D. V. Iosifescu, et al. (2005). "Brain MRI white matter hyperintensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (Part II)." Psychiatry Res 140(3): 301-7.

The objective of this study was to investigate the relative impact of brain white matter hyperintensities (WMHs), cardiovascular risk factors and elements of the one-carbon cycle metabolism (including serum folate, vitamin B12 and homocysteine levels) on the outcome of antidepressant treatment in non-elderly subjects with major depressive disorder (MDD). Fifty MDD subjects were administered brain magnetic resonance imaging (MRI) scans at 1.5 T to detect T2 WMHs. The severity of brain WMHs was classified with the Fazekas scale (range=0-3). We assessed cardiovascular risk factors in all MDD subjects (age, gender, smoking, diabetes, family history, hypertension, cholesterol). MDD patients also had serum folate, vitamin B12 and homocysteine levels measured. All MDD subjects received treatment with fluoxetine 20 mg/day for 8 weeks. In a logistic regression, the severity of subcortical WMHs and the presence of hypofolatemia were independent predictors of lack of clinical response to antidepressant treatment. Separately, hypofolatemia also predicted lack of remission to antidepressant treatment. These associations were independent of the presence of smoking, diabetes, family history, hypercholesterolemia, hyperhomocysteinemia and low B12 levels. Although preliminary, the results of the present work suggest that subcortical brain WMHs and hypofolatemia may have an independent negative impact on the likelihood of responding to antidepressant treatment in non-geriatric subjects with MDD.

Papakostas, G. I., T. Petersen, et al. (2005). "The relationship between serum folate, vitamin B12, and homocysteine levels in major depressive disorder and the timing of improvement with fluoxetine." Int J Neuropsychopharmacol 8(4): 523-8.

The objective of the present study was to examine the relationship between serum folate, vitamin B12, and homocysteine levels and the timing of clinical improvement to fluoxetine in major depressive disorder (MDD) patients. A total of 110 outpatients with MDD who responded to an 8-wk trial of fluoxetine had serum folate, B12, and homocysteine measurements at baseline (prior to fluoxetine initiation). Onset of clinical improvement was defined as a 30% decrease in Hamilton Depression Scale scores that led to a 50% decrease by week 8. Patients with low folate levels (<or=2.5 ng/ml) were more likely to experience a later onset of clinical improvement than eufolatemic patients (p =0.0028). B12 and homocysteine level status did not predict time to clinical improvement (p >0.05). In conclusion, low serum folate levels were found to be associated with a delayed onset of clinical improvement during treatment with fluoxetine in MDD by, on average, 1.5 wk.

Papakostas, G. I., T. Petersen, et al. (2004). "Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 2: predictors of relapse during the continuation phase of pharmacotherapy." J Clin Psychiatry 65(8): 1096-8.

OBJECTIVE: In the present study, we assessed the relationship between serum folate, vitamin B12, and homocysteine levels on the rate of relapse in outpatients with remitted major depressive disorder (MDD) during a 28-week continuation phase of treatment with fluoxetine. METHOD: Seventy-one outpatients (mean +/- SD age = 40.2 +/- 11.1 years; 56.3% women) with MDD (as assessed with the Structured Clinical Interview for DSM-III-R) who had remitted and who were enrolled in the continuation phase of treatment with fluoxetine had serum folate, vitamin B12, and homocysteine measurements completed at baseline (prior to acute-phase treatment). Patients were followed for 28 weeks of continued treatment with fluoxetine 40 mg/day to monitor for depressive relapse. Folate levels were classified as either low (< or = 2.5 ng/mL) or normal. Vitamin B12 levels were classified as either low (< or = 200 pg/mL) or normal. Homocysteine levels were classified as either elevated (> or = 13.2 micromol/L) or normal. With the use of separate logistic regressions, we then assessed the relationship between folate, vitamin B12, and homocysteine level status and relapse. The study was conducted from November 1992 to January 1999. RESULTS: The presence of low serum folate levels (p =.004), but not low B12 (p >.05) or elevated homocysteine levels (p >.05), was associated with relapse during continuation treatment with fluoxetine. The relapse rates for patients with (N = 7) and without (N = 64) low folate levels were 42.9% versus 3.2%, respectively. CONCLUSION: Low serum folate levels were found to place patients with remitted MDD at risk for depressive relapse during the continuation phase of treatment with fluoxetine.

Papakostas, G. I., T. Petersen, et al. (2004). "Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression." J Clin Psychiatry 65(8): 1090-5.

OBJECTIVE: In the present study, we assessed the relationship between serum folate, vitamin B12, and homocysteine levels and clinical response in patients with major depressive disorder (MDD) who had previously failed to respond to open treatment with fluoxetine 20 mg/day and were enrolled in a 4-week, double-blind trial of either (1) fluoxetine dose increase, (2) lithium augmentation of fluoxetine, or (3) desipramine augmentation of fluoxetine. METHOD: Fifty-five outpatients (mean +/- SD age = 41.7 +/- 10.6 years; 50.9% women) with MDD as assessed with the Structured Clinical Interview for DSM-III-R who were enrolled in the double-blind trial had serum folate, vitamin B12, and homocysteine measurements completed at baseline (prior to fluoxetine treatment initiation). Folate levels were classified as either low (< or = 2.5 ng/mL) or normal. Vitamin B12 levels were classified as either low (< or = 200 pg/mL) or normal. Homocysteine levels were classified as either elevated (> or = 13.2 micromol/L) or normal. With the use of a logistic regression, we then assessed the relationship between (1) low or normal folate levels, (2) normal or low B12 levels, and (3) elevated or normal homocysteine levels and clinical response to double-blind treatment. The study was conducted from November 1992 to January 1999. RESULTS: Low serum folate levels (chi2=3.626, p =.04), but not elevated homocysteine (p >.05) or low vitamin B12 levels (p >.05), were associated with poorer response to treatment. The response rates for patients with (N = 14) and without (N = 38) low folate levels were 7.1% versus 44.7%, respectively. CONCLUSION: Low serum folate levels were found to be associated with further treatment resistance among patients with fluoxetine-resistant MDD.

Paul, I. A. and P. Skolnick (2003). "Glutamate and Depression: Clinical and Preclinical Studies." Ann NY Acad Sci 1003(1): 250-272.

The past decade has seen a steady accumulation of evidence supporting a role for the excitatory amino acid (EAA) neurotransmitter, glutamate, and its receptors in depression and antidepressant activity. To date, evidence has emerged indicating that N-methyl-d-aspartate (NMDA) receptor antagonists, group I metabotropic glutamate receptor (mGluR1 and mGluR5) antagonists, as well as positive modulators of {alpha}-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors have antidepressant-like activity in a variety of preclinical models. Moreover, antidepressant-like activity can be produced not only by drugs modulating the glutamatergic synapse, but also by agents that affect subcellular signaling systems linked to EAA receptors (e.g., nitric oxide synthase). In view of the extensive colocalization of EAA and monoamine markers in nuclei such as the locus coeruleus and dorsal raphe, it is likely that an intimate relationship exists between regulation of monoaminergic and EAA neurotransmission and antidepressant effects. Further, there is also evidence implicating disturbances in glutamate metabolism, NMDA, and mGluR1,5 receptors in depression and suicidality. Finally, recent data indicate that a single intravenous dose of an NMDA receptor antagonist is sufficient to produce sustained relief from depressive symptoms. Taken together with the proposed role of neurotrophic factors in the neuroplastic responses to stressors and antidepressant treatments, these findings represent exciting and novel avenues to both understand depressive symptomatology and develop more effective antidepressants.

Peet, M. (2004). "International variations in the outcome of schizophrenia and the prevalence of depression in relation to national dietary practices: an ecological analysis." Br. J. Psychiatry 184(5): 404-408.

Background Dietary variations are known to predict the prevalence of physical illnesses such as diabetes and heart disease but the possible influence of diet on mental health has been neglected. Aims To explore dietary predictors of the outcome of schizophrenia and the prevalence of depression. Method Ecological analysis of national dietary patterns in relation to international variations in outcome of schizophrenia and prevalence of depression. Results A higher national dietary intake of refined sugar and dairy products predicted a worse 2-year outcome of schizophrenia. A high national prevalence of depression was predicted by a low dietary intake of fish and seafood. Conclusions The dietary predictors of outcome of schizophrenia and prevalence of depression are similar to those that predict illnesses such as coronary heart disease and diabetes, which are more common in people with mental health problems and in which nutritional approaches are widely recommended. Dietary intervention studies are indicated in schizophrenia and depression.

Russo, S., I. P. Kema, et al. (2003). "Tryptophan as a Link between Psychopathology and Somatic States." Psychosom Med 65(4): 665-671.

OBJECTIVE: Several somatic illnesses are associated with psychiatric comorbidity. Evidence is provided that availability of the essential amino acid tryptophan, which is the precursor of serotonin, may cause this phenomenon. METHODS: We performed a database search to find relevant articles published between 1966 and 2002. For our search strategy, we combined several diseases from the categories hormonal, gastrointestinal, and inflammatory with the search terms "tryptophan" and "serotonin." RESULTS: The catabolism of tryptophan is stimulated under the influence of stress, hormones and inflammation by the induction of the enzymes tryptophan pyrrolase (in the liver) and IDO (ubiquitous). Because of the reduction in blood levels of tryptophan under these circumstances the formation of cerebral serotonin is decreased. CONCLUSIONS: It is argued that the coupling of peripheral tryptophan levels and cerebral serotonin levels has physiological significance. The clinical implications and therapeutic consequences of changes in tryptophan and consequently serotonin metabolism are discussed.

Sachdev, P. S., R. A. Parslow, et al. (2005). "Relationship of homocysteine, folic acid and vitamin B12 with depression in a middle-aged community sample." Psychol Med 35(4): 529-38.

BACKGROUND: Case control studies have supported a relationship between low folic acid and vitamin B112 and high homocysteine levels as possible predictors of depression. The results from epidemiological studies are mixed and largely from elderly populations. METHOD: A random subsample of 412 persons aged 60-64 years from a larger community sample underwent psychiatric and physical assessments, and brain MRI scans. Subjects were assessed using the PRIME-MD Patient Health Questionnaire for syndromal depression and severity of depressive symptoms. Blood measures included serum folic

acid, vitamin B12, homocysteine and creatinine levels, and total antioxidant capacity. MRI scans were quantified for brain atrophy, subcortical atrophy, and periventricular and deep white-matter hyperintensity on T2-weighted imaging. RESULTS: Being in the lowest quartile of homocysteine was associated with fewer depressive symptoms, after adjusting for sex, physical health, smoking, creatinine, folic acid and B12 levels. Being in the lowest quartile of folic acid was associated with increased depressive symptoms, after adjusting for confounding factors, but adjustment for homocysteine reduced the incidence rate ratio for folic acid to a marginal level. Vitamin B12 levels did not have a significant association with depressive symptoms. While white-matter hyperintensities had significant correlations with both homocysteine and depressive symptoms, the brain measures and total antioxidant capacity did not emerge as significant mediating variables. CONCLUSIONS: Low folic acid and high homocysteine, but not low vitamin B12 levels, are correlates of depressive symptoms in community-dwelling middle-aged individuals. The effects of folic acid and homocysteine are overlapping but distinct.

Schneider, B., B. Weber, et al. (2000). "Vitamin D in schizophrenia, major depression and alcoholism." J Neural Transm 107(7): 839-42.

25-Hydroxyvitamin D3, 1,25-dihydroxyvitamin D3, calcium, phosphate and parathyreoidal hormone levels were assessed in 34 patients with schizophrenia (DSM-III-R, 44% female, mean age 38.9 +/- 2.1 years), 30 patients with alcohol addiction (16% female, mean age 48.7 +/- 2.2 years), 25 patients with major depression (56% female, mean age 57.6+/- years) and 31 healthy controls. Only 25-hydroxyvitamin D3 and 1,25-dihydroxvitamin D3 levels were significantly lower in all groups of psychiatric patients than in normal controls, but not phosphate, calcium and parathyreoidal hormone levels. Significant differences in the vitamin D levels could not be found between the three psychiatric groups. These findings do not support the idea that vitamin D is specifically involved in the pathophysiology of depression. The difference in patients as compared to the healthy controls might be related to a different social background resulting in differing habits e.g. of nutrition.

Scott, T. M., K. L. Tucker, et al. (2004). "Homocysteine and B Vitamins Relate to Brain Volume and White-Matter Changes in Geriatric Patients With Psychiatric Disorders." Am J Geriatr Psychiatry 12(6): 631-638.

Objective: There is a growing literature on the relationship between low serum B-vitamins, elevated homocysteine, and cognitive impairment; however, few studies have examined radiological markers of associated neuropathology in geropsychiatry inpatients. The authors examined the relationship of homocysteine, folate, and vitamin B12 with magnetic resonance imaging (MRI) markers of neuropathology. Methods: In this archival study, authors reviewed the MRIs and medical records of 34 inpatients in a geriatric psychiatry unit. Patients were selected if folate, B12, and/or homocysteine levels had been assessed and if the appropriate clinical MRIs were performed (19 men; mean age, 75 years). Patients with schizophrenia or current substance dependence were excluded. The relationships between MRI volume measures, white-matter hyperintensity (WMH) grade, and serum concentrations of folate, B12, and homocysteine were analyzed, using age-adjusted Pearson correlations. Results: Homocysteine was related to WMH grade, but not brain-volume measures. Folate was associated with hippocampus and amygdala, and negatively associated with WMH. B12 level was not statistically associated with any brain measure. Conclusions: Elevated homocysteine and low folate were associated with radiological markers of neuropathology. Since no patient had clinically deficient folate, it may be important to rethink what defines functionally significant micronutrient deficiency and explore what this means in different age- and health-status groups. Larger samples will be needed to assess interactions between homocysteine, micronutrients, and other neuropathology risk factors.

Shahidi, F. and H. Miraliakbari (2005). "Omega-3 fatty acids in health and disease: part 2--health effects of omega-3 fatty acids in autoimmune diseases, mental health, and gene expression." J Med Food 8(2): 133-48.

Omega-3 fatty acids from marine and plant sources provide a wide range of benefits in several human health conditions. In vivo studies indicate that omega-3 fatty acids influence the course of several human diseases, including those that involve abnormal immune function, mental disorders, and genetic abnormalities in lipid metabolism. Omega-3 fatty acids are taken up by virtually all body cells and affect membrane composition, eicosanoid biosynthesis, cell signaling cascades, and gene expression. These fatty acids are especially important during human brain development; maternal deficiency of omega-3 fatty acids may lead to several neurological disorders. The review highlights recent findings on omega-3 fatty acids' influence on autoimmune diseases, mental health, and gene expression.

Shi, Q., J. E. Savage, et al. (2003). "L-Homocysteine Sulfinic Acid and Other Acidic Homocysteine Derivatives Are Potent and Selective Metabotropic Glutamate Receptor Agonists." J. Pharmacol. Exp. Ther. 305(1): 131-142.

Moderate hyperhomocysteinemia is associated with several diseases, including coronary artery disease, stroke, Alzheimer's disease, schizophrenia, and spina bifida. However, the mechanisms for their pathogenesis are unknown but could involve the interaction of homocysteine or its metabolites with molecular targets such as neurotransmitter receptors, channels, or transporters. We discovered that L-homocysteine sulfinic acid (L-HCSA), L-homocysteic acid, L-cysteine sulfinic acid, and L-cysteic acid are potent and effective agonists at several rat metabotropic glutamate receptors (mGluRs). These acidic homocysteine derivatives 1) stimulated phosphoinositide hydrolysis in the cells stably expressing the mGluR1, mGluR5, or mGluR8 (plus G[alpha]qi9) and 2) inhibited the forskolin-induced cAMP accumulation in the cells stably expressing mGluR2, mGluR4, or mGluR6, with different potencies and efficacies depending on receptor subtypes. Of the four compounds, L-HCSA is the most potent agonist at mGluR1, mGluR2, mGluR4, mGluR5, mGluR6, and mGluR8. The effects of the four agonists were selective for mGluRs because activity was not discovered when L-HCSA and several other homocysteine derivatives were screened against a large panel of cloned neurotransmitter receptors, channels, and transporters. These findings imply that mGluRs are candidate G-protein-coupled receptors for mediating the intracellular signaling events induced by acidic homocysteine derivatives. The relevance of these findings for the role of mGluRs in the pathogenesis of homocysteine-mediated phenomena is discussed.

Spillmann, M. K., A. J. Van der Does, et al. (2001). "Tryptophan depletion in SSRI-recovered depressed outpatients." Psychopharmacology (Berl) 155(2): 123-7.

RATIONALE: Recently, a number of studies have challenged the finding that acute tryptophan depletion (TD) increases depressive symptoms in medicated, formerly depressed patients. The present study examined the effects of acute nutritional TD on remitted depressed patients currently treated with selective serotonin reuptake inhibitors. In an attempt to clarify conflicting earlier findings, the effects of a number of clinical variables on outcome were also investigated. METHODS: Ten patients underwent TD in a double-blind, controlled, balanced crossover fashion. The control session followed the procedure of Krahn et al. (1996 Neuropsychopharmacology 15:325-328). Sessions were 5-8 days apart. RESULTS: TD was significantly related to increased scores on clinician-rated depression and anxiety scales, and on self-rated depression, anxiety, and somatic symptoms. The control challenge had no effect, despite the fact that the reductions in plasma tryptophan during the control session were unexpectedly high. Some evidence was found for a threshold in the relationship between reduction of plasma tryptophan and mood response. CONCLUSIONS: The mood effect of TD in medicated, formerly depressed patients was confirmed. A threshold may exist for mood effects following TD, implying that recent negative findings may have been caused by insufficient depletion. No other predicting or mediating factors were identified, although the variable "history of response pattern to medication" deserves further study.

Williams, A.-l., A. Cotter, et al. (2005). "The role for vitamin B-6 as treatment for depression: a systematic review." Fam. Pract. 22(5): 532-537.

Background. Major depression is the leading cause of disability worldwide, and among the 10 most frequent indications for using alternative medicine therapies, especially dietary supplements. Objective. To assess the evidence evaluating vitamin B-6 supplementation as treatment for depression. Methods. Medline, Psychinfo, AMED, and Cochrane Controlled Trials Register were searched from database inception through September 2001. All randomized controlled trials, controlled clinical trials, intervention studies, case-control studies, reviews, and case reports examining the evidence behind vitamin B-6 in depression among humans were selected. No limits were placed for demographics or co-morbidities. Only English language papers were abstracted and assessed for trial quality. Two abstractors independently evaluated each study, then reconciled findings. As data were available, between group treatment effect size was noted or, as needed, calculated. When studies reported outcome effects using multiple measures, data were abstracted to permit the greatest possible comparisons among papers. Results. Ten articles met inclusion criteria; three reviews, one case report, five RCTs, and one intervention study. There was no common outcome measure among all studies, eliminating opportunity for direct comparison of effect sizes. As an alternate means of comparison, effects were plotted as they related to the null hypothesis. Conclusion. Viewed as a whole, meaningful

treatment effect of vitamin B-6 for depression in general was not apparent. However, examination of papers addressing depression in pre-menopausal women only, reveals a consistent message about the value of using vitamin B-6 supplementation. Further study of vitamin B-6 as independent and adjuvant therapy for hormone related depression in women is indicated.