



a healthier model of healthcare

MAINE'S CENTER FOR FUNCTIONAL MEDICINE AND THE HEALING ARTS

Omega 3 Essential Fatty Acids, Vitamin B12 and Folate Supplementation Versus Fluoxetine for Depression

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(Omega-B)

Principal Investigator

Benedict Joseph Semmes MD

Director of Research

True North Health Center

202 U.S. Route One, Suite 202

Falmouth, Maine 04105

Department of Medicine

Maine Medical Center

(Note study did not go forward because of a new UK Bristol study showing no effect of Omega3s EPA:DHA 1.5 gms/ day for mild-mod depression at 3 months appears to answer, negatively, the most important question of the Omega-B trial.)

Abstract

Research Plan

- 1. Specific Aim**
- 2. Background and Significance**
- 3. Research Design and Methods**
- 4. Human Subjects**
- 5. Consultants/Collaborators**
- 6. Literature Cited**

Personnel Engaged, including consultants, collaborators

Detailed Budget for Initial Budget Period

Budget for Entire Proposed Project Period

Biographical Sketch-Principal Investigator

Other Support

Resources and Environment

Abstract

Adults with **mild or moderate** major depression, screened from outpatient practices using a two-question technique, will be randomized to receive either supplementation with Omega-3 fatty acids eicosopentanaeonic acid (EPA) , docosohexanaeonic acid (DHA), Vitamin B-12 , intrinsic factor and folate or standard treatment with fluoxetine. Response to treatment will be measured using the Patient Health questionnaire -9 (phq-9) to assess level of depressed mood and the DYNAmic Short Form-36 (DYNA-SF-36) metric, to assess the impact on physical and emotional functioning one, three and six months later.

Research Plan

1. Specific Aims

(80 patients to complete to 3 months for significance, 192 to be enrolled to compensate for expected attrition. ^{1 2})

Test Hypotheses:

- 1) Giving Omega-3 FA, folate and B12 supplementation will reduce phq9 scores for depression.
- 2) A change in inflammatory markers is associated with response to omega-3 or folate-B12, intrinsic factor supplementation.
- 3) A change in serum levels of B12 and folate correlates with improved phq-9 score.

Research Questions:

For adults with **mild or moderate** major depression, does taking daily supplementation of a high quality EPA-rich omega-3 fatty acid taken in conjunction with a folate-B12-intrinsic factor supplement, when compared to fluoxetine 20 mg per day³, safely improve depression scores (phq9) at 3 months? Further, does it improve emotional and physical functioning as measured by the DYNAmic SF-36 quality of life metric, reduce hospitalization days or missed work days or suicidal ideation? Further, does response correlate with either marker of inflammation, Interleukin-6 or hsCRP?

2. Research Design and Methods

Study Design: prospective, randomized double-blinded, stratified, controlled trial

Setting:

Maine Medical Center primary care setting
Family Medicine, Bucknam Road, *Craig Schneider MD*
Internal Medicine Clinic *Jane Pringle MD*
Integrative Medicine center, True North, Falmouth *Joe Semmes MD*
Women to Women Health Center Yarmouth, ME *Marcelle Pick RNP*
Also potentially:
Martins Point Health Care Primary Care Adult Medicine *Margaret Shepp MD*

Patient selection:

Diagnosis of Chief Complaint of depression or

Sampling design: 2 question screen:

"During the past month, have you often been bothered by feeling down, depressed or hopeless?"

"During the past month, have you often been bothered by having little interest or pleasure in doing things?"

If a patient answers "yes" to both, these two questions have a 96% sensitivity and 57% specificity for the diagnosis of depression. ^{4 5 6} If either or both answers are "yes", then use:

Patient health questionnaire (phq9) ⁷ to screen patients, interpreting results by "Use of the phq-9 to Make a Tentative Depression Diagnosis" (April 2006 www.depression-primarycare.org; and "Diagnosis and management of depression using the phq-9" (MaineHealth guidelines for professionals in mental health: Depression - clinical tools)

Exclusion criteria within phq-9 score: Patients with severe depression - those with phq9 scores greater than 15 - and the non- or minimally depressed - those with scores less than or equal to 9 will be excluded. The focus of the study will be on those scoring between 10-14 on the phq-9. If patients score greater than 15 or indicate "Functional Impairment" endorsed as "somewhat difficult" or greater on Question number 10, "systems are in place for adequate diagnosis, effective treatment and follow-up" according to the 2002 guidelines for depression screening of the United States Preventive Services Task Force. ⁸

Eligibility

18-80 years old

Inclusion Criteria

"yes" answer to either question in 2 question screen
Phq9 scores greater than 9 and less than 15
Capable of giving informed consent
Has given written informed consent

Exclusion Criteria

Previous psychiatric diagnoses and medical conditions contraindicated in study

- Active suicidal ideation or other safety issues that would render the candidate unsuitable
- Bipolar disorder
- Schizophrenia
- Schizofrom/Schizoaffective disorder
- Anorexia Nervosa
- Obsessive-compulsive disorder
- Psychotic depression
- Known poor or non-response to fluoxetine
- Depression caused by physical illness or medication (beta-blockers, phenytoin, corticosteroids, reserpine)
- Alzheimers or other dementia
- HIV/immunosuppressed
- Aspirin-sensitive asthma
- Parasite infection
- Bleeding disorder
- History of Seizure disorder
- Current pregnancy, lactation, child-bearing potential not practicing an adequate form of contraception
- Anemia, unless B12 level mid-normal or higher
- Blindness or history of hereditary blindness in the family (Leber's)
- Coronary artery stenting
- History of prostate cancer
- History of colonic adenomas
- OTHER MALIGNANCY Hx?
- LIVER DISEASE/CIRRHOSIS (fluoxetine is hepatically eliminated; liver disease increases elimination 1/2 life significantly)
- Any unstable medical or neurologic condition likely to interfere with depression treatment

Patient taking medications with risk of drug interactions in study

- Participants on antidepressants, antipsychotics or mood stabilizers
- Anticoagulant drugs (not including low dose aspirin 81 mg per day)
- Sumatriptin (Imitrex) for headaches

- Use of monoamine oxidase (MAO)inhibitors
- Cyclooxygenase inhibitors-NSAIDS, aspirin, without a 4 week washout
- PIMOZIDE- used for Tourette's (prolonged QT interval risk)

Dietary/supplement exclusion criteria

- Subjects with dietary intake > 3 gms total omega 3 PUFA qd at baseline- focused baseline diet history of omega-3 rich foods: fish, walnuts, ground flaxseed; B-12-rich: liver, kidney, clams; folate-rich foods: brewer's yeast, black-eyed peas, rice and wheat germs, soybeans, bran, kidney beans, folate-fortified cereals (eg Multigrain cheerios) MULTIVITAMIN??
- Prior supplementation with EPA/DHA , folate , B12, or SAME
- Fish allergy

Psychosocial exclusion criteria

- Not likely to complete 3 months- moving, undomiciled etc.
- Active Alcohol or drug abuse

Intervention:

Double blinded randomized placebo-controlled

All eligible patients will be:

Randomized to:

Arm One:

EPA-DHA 6:1 Enteric- coated 3 softgels per day (each with EPA 500 mg

and DHA 60-100 mg) *Metagenics tm* Purity certified fish oil omega -3 concentrate

AND

Intrinsi B12/Folate *Metagenics tm* containing:

Folate bioavailable(as folic acid, L-5 methyl THF, 5-formyl THF) 800 micrograms

B12 500 mg (as cyanocobalamin)

Intrinsic factor 20 mg

AND placebo/s for fluoxetine

Arm Two:

fluoxetine 20 mg q am (Introductory **first week** dose **10 mg/d**. Non-responders after **week 4** will have doses increased to **30 mg/d**⁹.

Subsequently, non-responders at **week 8** will have doses increased to **40mg/day**).

AND

placebo for EPA:DHA (paraffin, olive oil or low dose vitamin E capsules) **AND** placebo for Intrinsi-B12 folate

(probably delete this phase) Placebo Lead in:

All patients will receive placebo initially for one week. Those who experience a 20 % phq score reduction at one week will be discontinued from the study. This should represent fewer than 20% of patients ¹⁰.

Biomarkers:

Baseline, 3 months, 6 months- serum folate,^{11 12}, serum B12¹³, *Omega-3 index*¹⁴ in ten percent of patients to monitor compliance, interleukin 6, hsRP (markers for inflammation), CBC with platelet count, weight, blood pressure, episode bleeding, hospital admission for medical reasons

On enrollment, patients will receive a list of foods high in omega-3s, folate and B12. They will be advised to avoid excessive intake of these; and at the end of the study they will be surveyed about compliance.

Leukocyte samples will be frozen and saved for possible gene polymorphism analysis in three genes: MTHFR, COMT, serotonin transporter receptor.

Psychosocial markers:

Baseline, 1 week, 3 week, 6 week, 3 months, 6 months- Patients Health Questionnaire 9 (phq9)^{15 16 17 18 19}

Baseline, 3 week, 6 week, 3 months, 6 months DYNA SF 36²⁰
Days of Hospitalizations- psychiatric and other, days of missed work

Safety system:

Patients who score above 15 on the phq9 are may have severe depression and will be referred directly to appropriate counseling:

Ingraham
McGeachey Hall MMC
Community Counseling
Miles Simmons MD True North

Weekly phone contact both arms of age 18-24, otherwise biweekly²¹, for suicide risk factors , next of kin also will be contacted by phone.

Weekly SSRI-type symptoms²² screening- for 4 weeks then biweekly:

- activating (insomnia, nervousness, anxiety),
- sedating (somnia, asthenia),
- gastrointestinal (dyspepsia, nausea, anorexia, diarrhea)
- other symptoms-tremor, sweating, dizziness, headache

If phq9 score increases by > or = 4, refer for individual evaluation, consider withdrawing from study

Women of childbearing potential are required to have a negative serum pregnancy test (bHCG) and to use an oral contraceptive, IUD or barrier method of contraception during the entire study.

Predictor variables:

Fluoxetine
EPA-DHA extra strength and Intrinsic-B12 folate
Baseline Serum folate, B12, interleukin 6, hsCRP
Baseline Phq9 and DynaSF-36 scores

Confounding variables:

Psychotropic drugs
Psychotherapy
Non-pharmacologic treatments such as light therapy
Anti-inflammatories-drugs, foods
Dietary omega-3 intake
Dietary B12, folate intake
Single nucleotide polymorphisms-MTHFR, COMT (will freeze serum samples for later study)
Seasonal Affective Disorder (season of enrollment, daylength, Vitamin D levels)

Outcome variables:

Difference between Phq9 scores at baseline and at 3 months is the primary endpoint.

Differences between DynaSF-36 scores between baseline, 3 months and 6 months
Differences in Serum folate, B12, omega-3 index, interleukin 6, hsCRP, phq9 deltas
> or = 5

Suicidal ideation
Days of hospitalization, missed work over 3 and 6 months

Statistical Analysis:

- Hypotheses:
 - 4) Giving Omega-3 FA, folate and B12 supplementation will reduce phq9 scores for depression.
 - 5) A change in inflammatory markers is associated with response to omega-3 or folate-B12, intrinsic factor supplementation.
 - 6) A change in serum levels of B12 and folate correlates with improved phq-9 score.
- Stratification for each site with randomization to 2 arms
- Study is 90% powered with p value 0.05 significance using nQueryAdviser software-
 - a) A sample size of 39 in each group will have a 90% power to detect a difference in means of -3.500 (the difference between a Group 1 mean, μ_1 , of 8.900 and a Group 2 mean, μ_2 , of 12.400) assuming that the Group 1 standard deviation, σ_1 , is 3.700 and the Group 2 standard deviation, σ_2 , is 5.500 (the ratio of Group 1 standard deviation to Group 2 standard deviation is 1.486) using a two group Satterwaite t-test with a 0.050 two-sided significance level.²³ Sixty patients will be enrolled in each group to account for anticipated drop-outs. Special efforts will be employed to enhance retention.
 - b) This study assumes the psychometric properties of the phq9 are similar to the HAM-D 17 item scale, both in respect to responsiveness to change and to the variability relative to the difference between groups.
 - c) This study assumes unequal variances (that is the standard deviations from the two basis studies – one on fluoxetine effect at 8 weeks²⁴ and one on the Omega-3 fatty acid effect at 8 weeks²⁵ – were different).
- Multivariate regression-to neutralize confounders if randomization is not successful
- Intention to treat analysis
- External validity

Varied community settings-generalizable results

CONSORT Plus criteria (Consolidated Standards of Reporting Trials) Plus.
Also Reporting Randomized, Controlled Trials of Herbal Interventions: An Elaborated CONSORT Statement²⁶

Safety

The important theoretical risks of omega-3 fatty acids include bleeding from platelet inhibition, immune suppression and the precipitation of peripheral neuropathy in a patient with masked Vitamin B 12 deficiency, or a more remote increased risk of prostate cancer.

The anti-inflammatory role of omega-3 fatty acids could reduce immune response and increase the risk of infections. A dose of 4 gms of EPA per day and 0.9 gms DHA affects adversely neutrophil superoxide production in response to *E. Coli* by up to 20% in elderly, but not young men. Whether this is a clinically relevant impairment is not clear. Daily doses of 1.35 gms EPA and 0.3 gms DHA did not have any detrimental effects on innate immune functions in healthy young or older men.²⁷ Doses greater than 3 gm daily might decrease blood coagulation and increase the risk of bleeding.^{28 29} Six grams per day of DHA but not EPA effected platelet aggregation by ADP.³⁰

Sixteen patients on chronic warfarin therapy showed no effect of omega 3 PUFAs on international normalized ratios (INRs)at the dose range of 3-6 grams per day. Bleeding times or other assays of platelet function were not studied.³¹ According to a 1999 review by Simopoulos, EPA doses of at least 4 g/d are needed to increase bleeding times.³² There is some concern that very high doses of EPA can have a deleterious effect on cell membrane fatty acid profiles by displacing other fatty acids.³³ The FDA has advised that the safe upper limit of DHA/EPA intake is 3 gms/person/day including **both** supplement and conventional food sources, and suggests that omega 3 supplement labels recommend limiting the use of omega-3 supplements to two grams/day.³⁴

It is safer for patients to administer oral folate and vitamin B 12 together. This would be important to guard against the possibility of precipitating neuropathy in the setting of vitamin B 12 deficiency and pernicious anemia³⁵ Pernicious anemia is thought to be present in 2% of individuals over 60.³⁶ Most cases of this sort of neurologic progression in vitamin B₁₂ deficiency have been seen at doses of folic acid of 5,000 mcg (5 mg) and above. In order to be very sure of preventing irreversible neurological damage in B₁₂ deficient individuals, the Food and Nutrition Board of the Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 mcg (1 mg daily).³⁷ Undiagnosed pernicious anaemia is a common finding in the elderly, especially among black and white women; and 800,000 elderly in the U.S. may be at risk for masked Vitamin B12 deficiency if exposed to large doses of folate.³⁸ It has long been standard practice to administer Vitamin B-12 by intramuscular injection. Recent studies have shown that oral Vitamin B 12 can maintain an adequate serum level. A May 2005 Cochrane review concluded that "The evidence derived from these limited studies suggests that 2000 mcg doses of oral vitamin B12 daily and 1000 mcg doses initially daily and thereafter weekly and then monthly may be as effective as intramuscular administration in obtaining short term haematological and neurological responses in vitamin B12 deficient patients."^{39 40} A recent prospective study showed that high serum levels of B12 (the highest quintile) is associated with an increased risk of prostate cancer.^{41 42} Vitamin B12 might be a marker for increased animal fat consumption or some other agent which contributes to prostate cancer risk. An earlier, larger, non-prospective study found the relationship of B12 and folate to prostate cancer to be "null".

Adverse effects from or contraindications to from omega 3 PUFAs are rare, but according to the Natural Medicines Comprehensive Database (NMCD)⁴³, there is a case report of hypomania in a patient with major depression and other authors describe theoretical side effects of lowering blood pressure by vasodilation and interference with platelet aggregation. Pregnant women and patients on anticoagulant medication (warfarin, clopidogrel) are advised to avoid supplementation with omega-3 PUFAs, but concrete evidence to support this recommendation is sparse. A recent review suggested that omega-3 fatty acids might be an ideal treatment for depression in pregnancy.⁴⁴

Fluoxetine has several side effects associated with it, which are listed in order of frequency. The more common side effects are nausea (22% vs 9% placebo), anxiety/nervousness (14% vs 7% placebo), insomnia (28% vs 22% placebo), somnolence (12% vs 5% placebo), decreased appetite (11% vs 2% placebo), asthenia (11% vs 6% placebo), diarrhea (11% vs 7% placebo). (Data from package insert for Prozac, Eli Lilly)

Rare but serious risks of fluoxetine (and all SSRIs) are increased suicidality early on in treatment, serotonin syndrome, precipitation of seizures, and allergic events. SSRIs have recently been required to show a "black box" warning for adolescents, including up to age 24 for increased risk of suicide.

Patients in this study, especially ages 18-24, will be monitored closely for clinical worsening, signs of suicidality, or unusual changes in behavior. Serotonin syndrome is associated with concomitant use of serotonergic or triptan drugs, which will eliminate potential subjects from participating. Patients with a known history of seizures will be excluded from the study as well. Patients will be advised to contact their doctor or the research team, or go to the emergency department in the rare chance should they develop a severe rash or difficulty breathing after taking their assigned medications. Very rarely a lupus-like syndrome has been reported to follow an allergic reaction to fluoxetine.

There has also been some report of hyponatremia, but the lowest value was a serum sodium of 129, which was not clinically significant. Prolonged QT interval is an adverse event associated with overdose of fluoxetine.

Background and Significance

Depression is currently the fourth leading contributor to the global burden of disease (as measured using disability-adjusted life years) and will move into second place by 2020.⁴⁵ Omega-3 fatty acids, folate and vitamin B 12 are essential nutrients^{46 47} that show promise in mitigating the rising tide of depression. Sixteen percent of the adult U.S. population experience major depression; but only one in five is adequately treated.⁴⁸ Depression is the leading cause of death and disability in people aged 18 to 44 in the U.S.A.⁴⁹ Depression is one of the top five chronic disease causes of admissions to hospitals.⁵⁰ In general medical practice, at least 1 in 10 outpatients has major depression, but most cases are unrecognized or inappropriately treated.^{51 52} Depression affects the lives of the elderly more than physical illness.⁵³ While patients can be easily screened for depression currently more than a third of patients treated with antidepressants do not improve. A stepped approach to additional antidepressant treatment appears Star-D is the landmark study.

Disparate but converging lines of evidence for a role for omega-3 fatty acids in treating or preventing depression⁵⁴ are epidemiological (Dietary intake of omega-3 fatty acids is inversely related to depression^{55 56 57} biochemical, and supported by preliminary clinical trials. The mechanism is uncertain but may be related to their significant anti-inflammatory role in the arachidonic acid cytokine cascades^{58 59 60}. Total omega-3 fatty acid levels in plasma are associated with lower levels of inflammatory markers (IL-6, IL-1ra, and TNFalpha) and higher levels of anti-inflammatory markers (IL-6r, IL-10 and TGFbeta).⁶¹ Neurochemical studies of omega-3 fatty acids in animals have reported findings consistent with antidepressant action^{62 63}. Omega-3 fatty acids also inhibit protein kinase C activity, a site of antidepressant effects on serotonin receptors and transporters.^{64 65 66 67} DHA is the polyunsaturated fatty acid (PUFA) that predominates in brain synaptic membranes and is required for optimal neuronal function.⁶⁸ Depressed patients have less DHA in RBC membranes than controls⁶⁹, and lower omega-3 fatty acids levels in adipose tissue⁷⁰ and serum⁷¹. Abnormal metabolism of omega 3s, perhaps related to inflammation, occurs in depressed patients and may persist despite antidepressant treatment.⁷² Seasonal variation in depression, PUFA intake and suicide appear to correspond.⁷³ The ratio of arachidonic acid to EPA in red cell membranes correlates with severity of depression, and improving that ratio is a rationale for supplementation with EPA.⁷⁴ The ratio of omega 6 to omega 3 fats

may additionally reflect a pro- and anti-inflammatory seesaw. This ratio is increased in women with post-partum depression⁷⁵ and in community dwelling elderly.^{76 77}

Three of six double-blind, placebo-controlled trials have reported therapeutic benefit in either the primary or secondary statistical analysis, particularly when EPA is added on to existing psychotropic medication. Unipolar depression and bipolar disorder are considered distinct psychiatric conditions, although major depression occurs in both. Four of four trials showed improvement in depression scores among bipolar patients. (see Table 1)

Table 1. Omega-3 fatty acids in the treatment of depression: double blind, placebo controlled trials

Study	n	Dosage Regimen	Outcome
Nemets et al ⁷⁸		20 add-on; EPA 2g/day	EPA>placebo
Peet and Horrobin ⁷⁹	70	add-on, EPA 1, 2, and 4 g/day	EPA 1
Su et al ⁸⁰	28	add on: fish oil 9.6 g/day	fish oil> placebo
Marangell et al ⁸¹	36	mono DHA 2g/day	DHA=placebo
Keck et al ⁸²		add on EPA 6 g/day	EPA=placebo
Puri ⁸³ (case study)	1	add-on EPA 4 g/day	Rx-resistant dramatic improvement
Silvers et al ⁸⁴	77	add-on fish oil 8g/day EPA 0.6 g/day and DHA 2.4 g/d	fish oil=placebo olive oil
Depression Component Scales in Bipolar Patients			
Stoll ⁸⁵	30	add-on EPA 6.2 g/day, DHA 3.4 g/day	
Keck et al ⁸⁶	76	add-on EPA 1-2 g/day	EPA 1=2g, EPA plus DHA > placebo both > placebo
Osher ⁸⁷	12	add-on EPA 1.5-2g/day	(not RCT) 8/10 > 50% HAMD response
Frangou et al ⁸⁸	75	add-on EPA 1 or 2 g/day	EPA 1=2, both > placebo
Postpartem Freeman et al ⁸⁹	16	mono-"omega-3" 0.5-2.8 g/day	all sign.improvement No placebo
Borderline personality Zanarini et al ⁹⁰			

add-on=added to existing medication adapted from Peet and Stokes⁹¹

Ethyl-EPA 1 gm bid for only four weeks significantly improved Hamilton scores by week three when added to maintenance antidepressant therapy.^{92 93} One gram per day of ethyl-EPA, given over 12 weeks significantly impacted depression scores, and was as effective as 4 grams per day in 70 patients with standard medication-resistant depression.^{94 95} In a

small Taiwanese study, up to 6.6 grams per day of omega 3 PUFA supplementation was well tolerated and effective.⁹⁶ In a study of 30 patients with bipolar disease 9.6 grams per say of omega 3 PUFAs (vs olive oil placebo), was well tolerated, and an effective adjunctive treatment⁹⁷

High quality fish oil supplements do not pose the same risk of heavy metal exposure as eating mercury- concentrating fish such as tuna, shark, swordfish, tilefish and king mackerel.⁹⁸ Four recent small clinical trials showed improved depression scores when omega-3 fatty acids were added to conventional pharmaceutical treatment.^{99 100}

Dietary folate is inversely associated with depression.^{101 102} Vitamin B12 deficiency ranges in the elderly ranges from 10-43% and is associated with depression as well as cognitive dysfunction.^{103 104} Folate and vitamin B 12 are crucial for methylation in the biosynthetic pathways of brain myelin and biogenic amines. S-adenosylmethionine (SAmE) is the methyl donor in these folate- and Vitamin B12-dependent pathways. SAmE is effective as monotherapy in the treatment of depression^{105 106 107}. Folate also appears to be required for the synthesis of tetrahydro-biopterin, a cofactor in the synthesis of 5-HT (serotonin).¹⁰⁸ Folate interacts with riboflavin, B12 and B6 (along with SAmE) in one-carbon processes, nucleic acid metabolism and biogenic amine methylation. Folate is present in dark green leafy foods ("*foliage*") and often used to fortify cereals. However, it becomes more bioavailable in the form of a supplement than from foods.¹⁰⁹ Low folate but not low Vitamin-B or high homocysteine levels were associated with resistance to fluoxetine.¹¹⁰ and increased relapse rate.¹¹¹ Low serum folate levels are present in 30% of acutely admitted psychiatric patients.¹¹² Borderline or low red blood cell folate is present in one third of depressed patients; and three well designed trials showed that depressed patients had better responses to conventional antidepressants when they were supplemented with folate.^{113 114 115} (see Table 2) .

Table 2. Folate in the treatment of depression: double blind, placebo controlled trials

Study	n	Dosage Regimen	Outcome
Godfrey et al ¹¹⁶ folate>placebo	approx 20	add-on methylfolate 15 mg/day (if serum level<200microg/l)	
Coppen et al ¹¹⁷ folate>placebo	127	add-on folic acid 500 microg/day	in women
Passer et al ¹¹⁸ folate=placebo	96 demented	add-on 5-methyltetrahydrofolate 50mg/d folate=trazodone, both (if borderline or low serum folate) improved HAMD	In men
Guaraldi et al ¹¹⁹ 81% improved	20 elderly	mono 5MTHF (open label NO controls)	

Patients with the single nucleotide polymorphism methylene tetrahydrofolate reductase (MTHFR) C677T are at greater risk for depression and likely benefit from supplemental folate.^{120 121 122} One large study does not support this view¹²³. The potential unmasking of pernicious anemia, in the setting of vitamin B 12 deficiency or insufficiency can be mitigated by supplementing with oral vitamin B 12. There has been a meteoric rise in the use of nutritional supplements in the U.S., including omega-3 fatty acids and B vitamins. An emerging awareness of morbidity and mortality associated with properly prescribed pharmaceuticals, the importance of genomic polymorphisms, a renewed appreciation for nutrition in healthy functioning and the burgeoning supplement industry, and frustration

with impractical clinical trials ¹²⁴, suggest the time is ripe for a sufficiently powered controlled trial comparing these promising, inexpensive and safe interventions to standard treatment with the selective serotonin reuptake inhibitor (SSRI) fluoxetine.

Biographical Sketch-Principal Investigator

Benedict J Semmes M.D.

Home Address

71 Cloyster Road
South Portland, Maine 04106-5113
207 741-2747
207 741-2188 (fax)
bjsemmes@maine.rr.com

Place of Birth

Bremerhaven, Germany (of U.S. parents)

Date of Birth

October 20, 1949

Citizenship

U.S.

Professional Experience

1998 – present	Attending Emergency Medicine Mercy Hospital, Portland, Maine
2002-present	Consultant, Integrative and Complementary Medicine /Internal Medicine Director of Research True North Center for Health and Healing 202 U.S. Route One, Suite 200 Falmouth, Maine, 04105 www.truenorthhealthcenter.org Attending Physician, Department of Internal Medicine Mercy Hospital, Portland, Maine
1996-present	Courtesy Staff, Department of Internal Medicine Maine Medical Center, Portland, ME (no clinical privileges)
1998	Part-time Attending Emergency Medicine Speare Memorial Hospital, Plymouth, NH
1998-2004	Part-time Attending Emergency Medicine Southern Maine Medical Center, Biddeford,
1996-2001	Courtesy Staff Department of Emergency Medicine, Maine Medical Center, Portland, ME (no clinical privileges)
1986 - 1996	Full-time Attending Emergency Physician The Arlington Hospital Department of Emergency Medicine 1701 North George Mason Drive Arlington, Virginia 22205 703 558-6165 30,000 patient volume

Attending physician in a 17 bed Emergency Department with a separate Fast Track facility. Department functioned as a Level II trauma center and serves as the principal county EMS hospital. Diverse patient population including geriatric, pediatric, med/surg., ob/gyn and orthopedics. Arlington Hospital is a 350 bed not-for-profit community hospital and has an active cardiovascular program, labor and delivery as well as inpatient pediatrics and psychiatry.

- 1993 - 1997 Vice President
Board of Directors
Arlington Physicians Group, Ltd.
8101 Hinson Farm Road, Suite 318
Alexandria, Virginia 22306
703 - 360 - 7663

- 1992 - 1997 Board of Directors
American Medical Community Associates*
8101 Hinson Farm Road, Suite 318
Alexandria, Virginia 22306
703 - 360 - 7663
* billing and collection service

- 1983 - 1986 Full-time Attending Emergency Physician
The Mount Vernon Hospital
Mount Vernon, Virginia

- 1983 - 1984 Part-time Acting Director & Attending Intensivist,
Intensive Care Unit, Capitol Hill Hospital,
Washington, D.C.

- 1988 Flight Physician/Consultant
Travel Assistance International
Washington, D.C.

Medical Staff Assignments

Mercy Hospital:

- 1999-present Credentials Committee
- 2005-present Institutional Review Board (IRB)

The Arlington Hospital:

- 1988 - 1997 Intensive Care Unit Committee
- 1996 Infection Control Committee

The Mount Vernon Hospital:

- 1984 - 86 Chairman, Pharmacy and Dietetics Committee
Chairman, Institutional Review Board (IRB)
- 1983 - 86 Intensive Care Unit/Coronary Care Unit Committee

Licensure

<u>Initial Year</u>	<u>State</u>	<u>License #</u>	<u>Renewal Date</u>
1980	New York	142733	1982
1982	Pennsylvania	MD025905-E	12/31/94
1983	Washington, D.C.	14067	12/31/86
1983	Maryland	D29588	09/30/87
1983	Virginia	0101-35604	10/31/96
1997	Maine	014611	10/31/08
1998	New Hampshire	10222	06/30/02

Certification

<u>Initial Year</u>	<u>Status</u>	<u>Speciality Board</u>	<u>Date of Termination</u>
1979	Diplomate	National Board of Medical Examiners	N/A
1982	Diplomate	American Board of Internal Medicine	No expiration
1982	Certified	Advanced Cardiac Life Support	N/A
1983	Certified	Advanced Trauma Life Support	N/A
1999	Certified	Pediatric Advanced Life Support	N/A
1986	Diplomate	American Board of Emergency Medicine	1996
1997	Recertified	American Board of Emergency Medicine	2007
2006	Recertified	American Board of Emergency Medicine	2016
1987	Diplomate	Critical Care Medicine, American Board of Internal Medicine	1997
1998	Recertified	American Board of Internal Medicine	2008
1998	Recertified	Critical Care Medicine, American Board of Internal Medicine	2008

Education

<u>Yr. Attended</u>	<u>Institution</u>	<u>Degree Obtained</u>
1967 - 1968	Dartmouth College Hanover, NH 03755	
1971 - 1973	Dartmouth College	A.B. Biological Sciences
1974 - 1978	University of Cincinnati College of Medicine Cincinnati, OH 45221-0127	M.D.

Postgraduate Training

<u>Dates Attended</u>	<u>Institution/Chairman/Chief of Service</u>	<u>Type of Program</u>
1978 - 1979	St. Vincent's Hospital and Medical Center Of New York City Raymond Boller, M.D. 153 West 11th Street New York, New York 10011	Flexible Internship
1979 - 1981	St. Luke's - Roosevelt Hospital Center Columbia University Edward Dwyer, M.D. 59th and 9th Avenue New York, New York 11101	Internal Medicine Residency Clinical Fellow
1981 - 1983	Departments of Medicine and Anesthesiology University Health Center of Pittsburgh Ake Grenvik, M.D. Presbyterian University Hospital Pittsburgh, PA 15213	Critical Care Medicine Fellowship

Professional

1999-2001 Maine Medical Association
 1982 - 1997 Society of Critical Care Medicine

Societies

2004-present Society of Integrative Oncology
 1997 - present American College of Physicians- American Society of Internal Medicine, Maine Chapter
 1997 - present American College of Emergency Physicians, Maine Chapter
 1983 - present American College of Emergency Physicians, Fellow, 1987 - 1996
 Well-being Committee and Section Member
 2000-present ACEP Critical Care Committee 1985
 Virginia ACEP Committee on Finance and Reimbursement
 1987-1992 (Chair 1991-1992) Editor, Managed Care Section Newsletter, 1996
 Member, Managed Care Section
 Member, Air Medical Transport Section
 1980 - 1997 American College of Physicians, D.C. Chapter
 1982 - 1984 American Society of Parenteral and Enteral Nutrition
 1983 - 1987 Alexandria Medical Society
 1983 - 1987 American Medical Association

Public Service

2003 Honorary Editorial Board Member, *Evidence-Based Integrative Medicine* ISSN 1176-2330
 Editor, monthly wellness e-newsletter **The True North Tune-Up** (see www.truenorthhealthcenter.org "what's new")
 2003 Corporator, Hospice of Southern Maine
 2001-2002 Adviser Hope Garden Hospice effort; York County
 2000 Attending Internist Portland Street Clinic
 1999-present State Faculty, Maine Medical Association Initiative on Educating Physicians on End of Life Care, Maine
 1999-present Division of Integrative Care/Holistic Council (A group of practitioners and community members exploring evidence-based and creative approaches to healing and wellness)
 Mercy Hospital, Portland, Maine
 1999-present Advisory Board, Cancer Community Center, South Portland, Maine/ lecturer
 1997-2001 Lecturer, American Cancer Society Conferences
 1994 - 1997 Medicare Physician Advisory Committee, Blue Shield Pennsylvania (Xact)

1986 - 1994	Virginia Chapter of A.C.E.P. Committee on Health Finance (Chairman, 1987-1992)
1984 - 1986	Northern Virginia Emergency Medical Services Regional Committee on Standardization of Medical Protocols
1986	A.C.E.P. Critical Care Committee
1987	Instructor, Advanced Cardiac Life Support (AHA - Red Cross)
1988	A.C.E.P. Legislative Key Contact

Academic Service

Georgetown University School of Medicine

1988 - 1997	Clinical Instructor, Department of Emergency Medicine
1988 - 1997	Medical Students 4th year students rotation in Emergency Medicine 1st and 2nd year students rotation in Ambulatory Care
1996-1997	Supervising Attending, Department of Internal Medicine, for interns rotating through the emergency department at Arlington Hospital
2003-present	Lecturer, University of New England (Osteopathic), housestaff and students

Scholarship and Research

<u>Date</u>	<u>Institution/Chairman</u>	<u>Topic</u>
1973	NSF Research Assistant Dr. Joseph Mascarenhas SUNY, Albany	Radioimmunoassay for cyclic nucleotides
1974	Technician Genetic mapping of mutant tumor viruses Dr. Allan Granoff Laboratories of Virology and Immunology St. Jude Children's Hospital, Memphis	
1975	Assistant Lymphocyte stimulations by mitogens Dr. Richard Armentrout University of Cincinnati College of Medicine Department of Biochemistry	
1983	Ake Grenvik MD, Division of Critical Care Respiratory monitoring with inductive plethysmograph	University Hospitals of Pittsburgh
2002-present	Director of Research, True North	Small Group Patient tracking with

2002-present Director of Research, True North 2002-present Director of Research, Small Group Patient tracking with scrutiny tools:

Dynamic SF-36 outcomes
www.AmIhealthy.com
www.qualitymetrics.com

Publications

- 2006 Semmes BJ: Depression A Role for Fish Oil and B Vitamins? Review Article Evid Based Integrative Med 2(3):1
- 1984 Tobin MJ, Semmes BJ, Pinsky MR, Snyder JV, tube on Grenvik A: Influence of the endotracheal breathing pattern during weaning from mechanical ventilation. Am. Rev. Resp. Dis., 129: 106A; 1984.
- 1985 Semmes BJ, Tobin MJ: Subjective and objective measurement of tidal volume in critically ill patients. Chest, Vol. 87, No. 4, pp. 577-579, May 1985.
- 1986 Tobin MJ, Perez W, Guenther SM, Semmes BJ, Mador MJ, Allen SJ, Lodato RF, Dantzker DR: The pattern of breathing during successful and unsuccessful trials of weaning from mechanical ventilation. Am. Rev. Resp. Dis., 134: 1111 - 1118 1986.

Personal

Married, Elonide Caldwell Semmes

Children:

Shelby Leigh (Dec. 21, 1982)
Eleanor Caldwell, (October 23, 1993)
Benedict Joseph, (October 23, 1993)
Raphael James Taylor (January 20, 1982) custodial

Military Service:

1969 – 1971 U.S. Army, served in Vietnam, honorably discharged

March 21, 2006

bjsemmes@truenorthhealthcenter.org

¹ Expected attrition through placebo lead in <20% Su KP Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol. 2003 Aug;13(4):267-71.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=12888186

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=16160619&query_hl=1&itool=pubmed_docsum

³ Fluoxetine 20 mg/ day is a typical dose. Patients will be started on 10 mg/ day and if not improved in 1 week the dose will be increased to fluoxetine 20 mg/d (or placebo). Non-responders by at the end of week 3 will have their doses increased to 40 mg per day

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http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9229283

⁵ "During the past month, have you often been bothered by feeling down, depressed or hopeless?"

"During the past month, have you often been bothered by having little interest or pleasure in doing things?"

If your patient answers "yes" to both, these two questions have a 96% sensitivity and 57% specificity for the diagnosis of depression.

⁶ Whooley MA J Gen Inter Med 1997 Dec 12(12):789-790 Case-finding instruments for depression. Two questions are as good as many.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=9229283

⁷ Patient Health Questionnaire 9 <http://www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/questionnaire/>

⁸ www.ahrq.gov/clinic/uspstf/uspstfdepr.htm

⁹ Fluoxetine 20 mg/ day is a typical dose. Patients will be started on 10 mg/ day and if not improved in 1 week the dose will be increased to fluoxetine 20 mg/d (or placebo). Non-responders by at the end of week 4 will have their doses increased to 30 mg per day, and then 40mg/day at week 8 if still not responding at that time.

¹⁰ Su KP Omega-3 fatty acids in major depressive disorder. A preliminary double-blind, placebo-controlled trial. Eur Neuropsychopharmacol. 2003 Aug;13(4):267-71.

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Folate, vitamin B12, homocysteine, and the MTHFR 677C->T polymorphism in anxiety and depression: the Hordaland Homocysteine Study.

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Ramin V. Linked Promoter Region on Expression of Serotonin Transporter in the Human Brain Am J Psychiatry 2006 163: 48-51. [\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)



Ramin V.

Lower Serotonin Transporter Binding Potential in the Human Brain During Major Depressive Episodes Am J Psychiatry 2006 163: 52-58. [\[Abstract\]](#) [\[Full Text\]](#) [\[PDF\]](#)

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¹²⁴ **Depression tied to low folate levels**

Last Updated: 2007-07-10 13:00:44 -0400 (Reuters Health)

NEW YORK (Reuters Health) - Results of a new study confirm an association between folate levels and depression.

The study, a pooled look at various studies on the topic, showed that people with lower levels of the B vitamin had an increased risk of depression. Whether their low folate status caused the depression, however, is unknown.

"Our study is unique in that for the first time all the relevant evidence in this controversial area has been brought together," Dr. Simon Gilbody, of the University of York, in York, UK, said in a university statement. "Although the research does not prove that low folate causes depression, we can now be sure that the two are linked," he added.

Depression is quickly becoming the world's second most common cause of disability. Currently, up to 1 in 10 individuals suffers depression, which is one of the top reasons for visits to primary care providers.

Many depressed patients have also been found to have low folate levels -- a finding that contributes to hypotheses linking folate and depression. Another factor suggesting an association between the two is the body of research showing the benefits of folate supplementation in depression treatment. Other studies, however, have had contradictory findings.

To further explore the topic, Gilbody and his team reviewed 11 studies on the association between folate levels and depression. The studies involved a total of 15,315 mostly adult participants, 1,769 of whom had depression.

Confirming the results of smaller studies, individuals with low folate levels had up to a 55 percent increased risk for depression, the investigators report in the *Journal of Epidemiology and Community Health*.

This increased depression risk remained even when the researchers took into account factors that could confound the results, such as the reduced appetite and excessive alcohol drinking that has been associated with depression.

What's more, not only did study participants with low folate levels have an increased risk of depression, but the converse was also true. Depressed individuals had lower folate levels than their non-depressed peers, the report indicates.

"Folic acid is a cheap and commonly used food supplement, and the identification of low folate status as a plausible specific risk factor for depression raises the possibility of using folic acid supplementation or improved diet in the prevention and treatment of depression at the population level," Gilbody and his co-authors conclude.

SOURCE: Journal of Epidemiology and Community Health, July 2007.

Eduardo Siguel has used the Kennedy Krieger Institute and that's where I have sent most of our fatty acid profiles. That said, I am told that MetaMetrix provides a good analysis.

Antidepressants tied to bone loss in elderly

Last Updated: 2007-06-25 16:55:59 -0400 (Reuters Health)

NEW YORK (Reuters Health) - The use of selective serotonin reuptake inhibitors (SSRIs), such as Zoloft and Paxil, for treatment of depression is associated with abnormally rapid bone loss in men and women age 65 and older, according to two reports in the Archives of Internal Medicine.

Cell receptors for serotonin are present in bone, a discovery that has raised concern that SSRIs may affect bone metabolism.

In one study, Dr. Susan J. Diem, an epidemiologist at the University of Minnesota in Minneapolis, and her associates measured hip bone levels twice in 2722 women, first when the subjects' average age was 78 years, and again approximately 5 years later.

SSRIs were being used by 198 women. After accounting for health status, weight change, and other factors, bone levels in the hip decreased by 0.82 percent per year among SSRI users versus 0.47 percent per year among nonusers.

In the second study, Dr. Elizabeth M. Haney, a geriatrician at the Oregon Health and Science University in Portland, and her team analyzed data from men who were an average of 74 years old.

The estimated bone level was 3.9 percent lower at the hip and 5.9 percent lower at the lower spine among SSRI users compared with nonusers.

The both studies the researchers found that other classes of antidepressants had no effect on bone levels.

"The biological plausibility, the consistency of these two studies with each other and with previous studies, and the magnitude of the associations partially support" the hypothesis that SSRI use causes bone loss, Dr. Kenneth Saag states in his editorial, titled "Mend the Mind, but Mind the Bones!"

Saag, a rheumatologist at the University of Alabama at Birmingham, recommends that reasons for starting and continuing SSRI therapy should be carefully examined and consideration should be given to alternative treatments for depression.

Nonetheless, he adds, "Those who truly need SSRIs should continue to receive them despite potential bone concerns."

SOURCE: Archives of Internal Medicine, June 25, 2007.

Inflammation Depression

[Am J Psychiatry](#). 2005 Jan;162(1):175-7.

Increase in interleukin-1beta in late-life depression.

[Thomas AJ](#), [Davis S](#), [Morris C](#), [Jackson E](#), [Harrison R](#), [O'Brien JT](#).

School of Neurology, Neurobiology and Psychiatry and the Institute for Ageing and Health, University of Newcastle upon Tyne, UK. a.j.thomas@ncl.ac.uk

OBJECTIVE: Depression has been associated with increases in circulating cytokines in younger adults, and there is evidence for prefrontal inflammation in late-life depression. The authors tested the hypothesis that levels of cytokine interleukin-1beta (IL-1beta) would be higher in subjects with late-life major depression. **METHOD:** Serum levels of IL-1beta were measured in three groups of subjects who were older than 60: 19 subjects with major depression, 20 subjects with subsyndromal depression, and 21 healthy comparison subjects. The Montgomery-Asberg Depression Rating Scale and the Geriatric Depression Scale were used to assess severity of depression. **RESULTS:** Compared with healthy subjects, those with major depression had significantly higher levels of IL-1beta (170%); the higher levels of IL-1beta strongly correlated with current depression severity. There were no significant differences between subjects with subsyndromal depression and the other two groups. **CONCLUSIONS:** These findings support the existence of an inflammatory response, which may be state dependent, in late-life depression.

[Int Psychogeriatr](#). 2007 Oct;19(5):914-20. Epub 2007 Jan 4.

[Links](#)

Soluble cell adhesion molecules in late-life depression.

[Thomas AJ](#), [Morris C](#), [Davis S](#), [Jackson E](#), [Harrison R](#), [O'Brien JT](#).

School of Neurology, Neurobiology and Psychiatry, University of Newcastle upon Tyne, U.K. Institute for Ageing and Health, University of Newcastle upon Tyne, U.K. Older Persons Directorate, Gateshead Health NHS Trust, U.K.

Background: Late-life depression has been associated with vascular diseases and with increases in circulating cytokines and cell adhesion molecules in the prefrontal cortex. We hypothesized that soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) would be increased in late-life major depression. **Methods:** Serum levels of sICAM-1 and sVCAM-1 were measured in subjects over 60 with major depression (N = 23), subsyndromal depression (N = 20) and controls (N = 25). Depression severity was assessed using the Montgomery-Asberg (MDRS) and Geriatric Depression (GDS) rating scales. **Results:** There was no significant increase in sICAM-1 (p = 0.240) or sVCAM-1 (p = 0.600) in depression nor was there any correlation of either molecule with depression severity. Adjusting for differences in cognitive impairment did not alter these findings. There was also no difference between subjects with an early onset of depression (before 60) and those with late-onset depression. **Conclusions:** These findings do not provide evidence that previously reported increases in serum cytokines in depression are due to peripheral vascular disease. Although we assessed subjects for vascular diseases it is possible that subtle but important differences between groups may still have been present and may have contributed to our negative findings. Our results suggest central nervous system mechanisms, such as related to HPA axis activation, may be responsible for the enhanced inflammatory response in depression.

[Psychiatry Res](#). 1996 Oct 16;64(3):161-7.

[Links](#)

Indicators of immune activation in major depression.

[Sluzewska A](#), [Rybakowski J](#), [Bosmans E](#), [Sobieska M](#), [Berghmans R](#), [Maes M](#), [Wiktorowicz K](#).

Department of Adult Psychiatry, Karol Marcinkowski University of Medical Sciences in Poznan, Poland.

Immune-inflammatory markers and their correlations were examined in patients with major depression. Plasma concentrations of interleukin-6 (IL-6), soluble IL-6 receptor (sIL-6R), soluble interleukin-2 receptor (sIL-2R), transferrin receptor (TfR), C-reactive protein (CRP), and alpha 1-acid glycoprotein (AGP), as well as the microheterogeneity of AGP, were measured in 49 major depressed patients during an acute phase of the illness and compared with concentrations in 15 normal control subjects. Plasma concentrations of IL-6, sIL-6, sIL-2R, TfR, CRP, and AGP were significantly higher in major depressed patients than in healthy control subjects. Patients with higher values of AGP

microheterogeneity coefficient (AGP-RC > 1.5) had significantly higher concentrations of AGP, IL-6, and TfR. The correlations between cytokines and acute phase proteins studied point to a significant role of elevated IL-6 secretion in the induction of Type I AGP microheterogeneity changes that are characteristic of some inflammatory conditions.

[JAMA](#). 2006 Mar 22;295(12):1412-9.
[Links](#)

Comment in:

[JAMA](#). 2006 Aug 23;296(8):931-2; author reply 932.

Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women.

[Mora S](#), [Lee IM](#), [Buring JE](#), [Ridker PM](#).

Donald W. Reynolds Center for Cardiovascular Research, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass 02215, USA. smora2@partners.org

CONTEXT: There are few data directly comparing the effects of physical activity and body weight on cardiovascular biomarkers. OBJECTIVE: To examine the association of physical activity and body mass index (BMI, defined as weight in kilograms divided by the square of height in meters) alone and in combination with cardiovascular biomarkers. DESIGN, SETTING, AND PARTICIPANTS: Cross-sectional analysis of 27,158 apparently healthy US women (mean age, 54.7 years) at the time of enrollment (1992-1995) in the Women's Health Study, a randomized, double-blind, placebo-controlled trial of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease and cancer. MAIN OUTCOME MEASURES: The association of physical activity and BMI with high-sensitivity C-reactive protein (CRP), fibrinogen, soluble intracellular adhesion molecule 1 (ICAM-1), homocysteine, low- and high-density lipoprotein (LDL and HDL) cholesterol, total cholesterol, apolipoprotein A-1 and B100, lipoprotein(a), and creatinine. RESULTS: Lower levels of physical activity and higher levels of BMI were independently associated (P for trend <.001) with adverse levels of nearly all lipid and inflammatory biomarkers. High BMI showed stronger associations with these biomarkers than physical inactivity. For example, using the reference group of physically active, normal weight women (energy expenditure > or =1000 kcal/week; BMI, 18.5-24.9) and adjusting for age, race, smoking, blood pressure, diabetes, menopausal status, and hormone use, the odds ratios (95% confidence intervals [CIs]) for having CRP >3 mg/L were: for inactive, normal weight women 1.26 (1.15-1.37); active, overweight 2.68 (2.41-2.98); inactive, overweight 3.11 (2.84-3.41); active, obese 8.25 (7.15-9.51); and inactive, obese 9.86 (8.84-10.99). In similar analyses, the odds ratios (95% CIs) for having HDL cholesterol <50 mg/dL were 1.20 (1.11-1.30); 2.25 (2.04-2.49); 2.62 (2.41-2.85); 4.21 (3.68-4.81); and 5.27 (4.77-5.84), respectively, and for having apolipoprotein B100 >120 mg/dL they were 1.21 (1.11-1.33); 1.86 (1.66-2.08); 2.06 (1.88-2.67); 2.35 (2.04-2.70); and 2.33 (2.09-2.59). Fibrinogen, ICAM-1, apolipoprotein A1, total cholesterol, and LDL cholesterol showed similar associations. By contrast, homocysteine, lipoprotein (a), and creatinine showed weak or nonsignificant associations. CONCLUSIONS: High BMI was more strongly related to adverse cardiovascular biomarker levels than physical inactivity. However, within BMI categories, physical activity was generally associated with more favorable cardiovascular biomarker levels than inactivity

<http://www.psychosomaticmedicine.org/cgi/content/full/66/5/679>

Several previous studies have examined the relationship between depression and CRP ([15,17-22](#)). However, much of the literature to date has been limited by retrospective, case-control study design and potential uncontrolled confounding ([15,18,19](#)). In addition,

very few studies have examined the relationship between depression and CRP in a healthy, nonelderly population ([21,22](#)).