Health Benefits of Nutritional Supplements

Selected Abstracts

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Forward

The importance of nutrition for human health has long been recognized. Prior to 1960, interest in this field largely focused on the etiology and prevention of acute nutrient deficiency diseases such as scurvy, rickets, and pellagra. Some 50 essential nutrients (vitamins, minerals, antioxidants, cofactors, essential amino acids, essential fatty acids) were identified, and recommended daily intakes for those essential nutrients (e.g. Recommended Dietary Allowances or RDAs) were developed. These recommendations, in turn, proved to be valuable in eradicating acute nutrient deficiency diseases.

During the past 20-30 years, attention has shifted to the role of diet and nutrition in the pathogenesis of chronic degenerative diseases. Heart disease, some cancers, osteoporosis, type II diabetes, and macular degeneration are all known to have dietary risk factors, many of which involve chronic nutrient deficiencies. Importantly, these associations have been much more difficult to study, in large measure because of the time frames involved. Chronic degenerative diseases develop over decades (lifetimes), and it is extremely challenging to conduct research programs for such extended periods. Nevertheless, advances in epidemiological and clinical research have helped us learn a great deal about the impacts (positive and negative) of diet and essential nutrient intakes on long-term health.

During the past decade, the scientific and healthcare communities have paid increasing attention to the role of nutritional supplements (as components of diet) in preventing and treating chronic disease. Hundreds of scientific studies have been conducted and published. These studies span a broad range of health issues. They have employed a wide variety of methodologies. And they have produced both positive and negative results. In some areas (e.g. the role of calcium and vitamin D supplements in slowing the progression of osteoporosis, and the role of folic acid supplements in preventing certain birth defects), results have been consistent, and benefits have been well accepted. In other areas (e.g. the role of antioxidant supplementation in preventing heart disease), results have been less consistent, and conclusions remain controversial. In any event, research on the health benefits of nutritional supplements is progressing, and evidence continues to mount that nutritional supplements offer a convenient and cost effective means for promoting health, over both the short- and long-terms.

The following is a collection of abstracts from about 100 scientific papers describing research on the health benefits of nutritional supplements. This collection is not exhaustive. Papers were selected on the basis of scientific merit and relevance to the field. The majority describes positive results, but in some, negative results are reported. Our objective in compiling this list was to provide readers with a good cross section of the scientific literature so that they could develop a sense for the current state of research in this field and draw their own conclusions concerning the role of supplementation in healthcare. References for many more papers are given in our bibliography entitled Health Benefits of Nutritional Supplements: Selected Readings .

For convenience, the abstracts have been sorted by health issue; namely Cardiovascular Health, Cancer Prevention, Strong Bones, Healthy Pregnancies/Healthy Babies, Sound Metabolism, Robust Immune Function, Acute Vision, and Other.

Cardiovascular Health

Chronic antioxidant use and changes in endothelial dysfunction: a review of clinical investigations.

Aminbakhsh A, Mancini J. 1999.
Can J Cardiol 15:895-903

There are tremendous clinical interest and speculation about the impact of reversing endothelial dysfunction. This paper reviews information from patient studies that have assessed the effect of chronic antioxidant use on endothelial dysfunction. A search of MEDLINE and Current Contents online, complemented by detailed analysis of references in the papers identified, was used to identify all studies pertaining to patients treated with oral antioxidants to modify endothelial dysfunction. Studies of single acute doses were excluded. Endothelium-mediated end points were vascular responses in conduit or resistance vessels, endothelial cell-monocyte interaction and measures of soluble adhesion molecules. Positive effects on conduit vessel dilation, endothelial cell-monocyte interactions and soluble adhesion molecules were common. Except for one study, negative effects were noted in resistance vessels. Further trials are required to clarify and define the impact of these findings on clinical outcome.

Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia.

Anderson JW, Davidson MH, Blonde L, Brown WV, Howard WJ, Ginsberg H, Allgood LD, Weingand KW. 2000.
Am J Clin Nutr 71(6):1433-8

BACKGROUND: Hypercholesterolemia is a major risk factor for coronary heart disease and nutrition management is the initial therapeutic approach. OBJECTIVE: This multicenter study evaluated the long-term effectiveness of psyllium husk fiber as an adjunct to diet in the treatment of persons with primary hypercholesterolemia. DESIGN: Men and women with hypercholesterolemia were recruited. After following an American Heart Association Step I diet for 8 wk (dietary adaptation phase), eligible subjects with serum LDL-cholesterol concentrations between 3.36 and 4.91 mmol/L were randomly assigned to receive either 5.1 g psyllium or a cellulose placebo twice daily for 26 wk while continuing diet therapy. RESULTS: Serum total and LDL-cholesterol concentrations were 4.7% and 6.7% lower in the psyllium group than in the placebo group after 24-26 wk ($P < 0.001$). Other outcome measures did not differ significantly between groups. CONCLUSIONS: Treatment with 5.1 g psyllium twice daily produces significant net reductions in serum total and LDL-cholesterol concentrations in men and women with primary hypercholesterolemia. Psyllium therapy is an effective adjunct to diet therapy and may provide an alternative to drug therapy for some patients.

Oral folate enhances endothelial function in hyperhomocysteinaemic subjects.

Bellamy MF, McDowell IF, Ramsey MW, Brownlee M, Newcombe RG, Lewis MJ. 1999.
Eur J Clin Invest 29:659-62

BACKGROUND: Elevated plasma homocysteine (Hcy) is a risk factor for vascular disease. A postulated mechanism is vascular endothelial damage by homocysteine. Hcy levels are inversely related to blood concentrations of folate and can be lowered by folate supplements. The effect of oral folic acid on endothelial function was investigated in healthy adults with mild hyperhomocysteinaemia. PATIENTS AND METHODS: Eighteen healthy subjects (Hcy > 13 micromol L-1 at entry), from a screening population of 890 volunteers, were entered into a randomised double-blind placebo-controlled crossover study of oral folic acid (5 mg daily for six weeks) with a six week interval between treatments. Flow-mediated (endothelium-dependent) and (endothelial-independent) glyceryl trinitrate (GTN)-mediated brachial artery dilatation were measured by high resolution wall tracking. RESULTS: Folate supplementation enhanced endothelium-dependent responses (+0.08 +/- 0.05 vs. +0.04 +/- 0.04 mm, P = 0.015) but endothelium-independent responses (GTN) were unchanged. Folate reduced Hcy (8.7 +/- 2.5 vs. 12.1 +/- 3.6 micromol L-1). CONCLUSION: High dose folic acid supplementation enhances endothelium-dependent vascular function and lowers plasma Hcy. This provides preliminary evidence that folate may have beneficial cardiovascular effects in adults with mild hyperhomocysteinaemia.

Effects of folic acid and combinations of folic acid and vitamin B-12 on plasma homocysteine concentrations in healthy, young women.

Bronstrup A, Hages M, Prinz-Langenohl R, Pietrzik K. 1998.
Am J Clin Nutr 68(5):1104-10

BACKGROUND: Elevated plasma homocysteine concentrations are considered to be a risk factor for vascular disease and fetal malformations such as neural tube defects. Recent studies have shown that plasma homocysteine can be lowered by folic acid in amounts corresponding to 1-2 times the recommended dietary allowance. Preliminary evidence indicates that vitamin B-12 may be beneficial when included in supplements or in a food-fortification regimen together with folic acid. OBJECTIVE: We aimed to compare the homocysteine-lowering potential of a folic acid supplement with that of 2 supplements containing different doses of vitamin B-12 in addition to folic acid. DESIGN: Female volunteers of childbearing age (n = 150) received a placebo for 4 wk followed by a 4-wk treatment with either 400 microg folic acid, 400 microg folic acid + 6 microg vitamin B-12, or 400 microg folic acid + 400 microg vitamin B-12. RESULTS: Significant reductions (P < 0.001) in plasma homocysteine were observed in all groups receiving vitamin treatment. The effect observed with the combination of folic acid + 400 microg vitamin B-12 (total homocysteine, -18%) was significantly larger than that with a supplement containing folic acid alone (total homocysteine, -11%) (P < 0.05). Folic acid in combination with a low vitamin B-12 dose (6 microg) affected homocysteine as well (-15%). CONCLUSIONS: These results suggest that the addition of vitamin B-12 to folic acid supplements or enriched foods maximizes the reduction of homocysteine and may thus increase the benefits of the proposed measures in the prevention of vascular disease and neural tube defects.

Dietary modulation of endothelial function: implications for cardiovascular disease.

Brown AA, Hu FB. 2001.
Am J Clin Nutr; 73:673-86

The vascular endothelium is the primary site of dysfunction in many diseases, particularly cardiovascular disease. A variety of risk factors, including smoking, hypercholesterolemia, hyperhomocysteinemia, hypertension, and diabetes mellitus, adversely affect endothelial function. Emerging evidence suggests an important role of dietary factors in modulating endothelial function. In particular, n-3 fatty acids, antioxidant vitamins (especially vitamins E and C), folic acid, and L-arginine appear to have beneficial effects on vascular endothelial function, either by decreasing endothelial activation or by improving endothelium-dependent vasodilation in patients at high risk of cardiovascular disease as well as in healthy subjects. These effects may serve as one potential mechanism through which these nutrients reduce the risk of cardiovascular disease, as observed in epidemiologic studies and several clinical trials. This article reviews clinical and experimental evidence regarding the role of these nutrients in modulating endothelial function and their potential to prevent cardiovascular disease.

Cholesterol-lowering effects of dietary fiber: a meta-analysis.

Brown L, Rosner B, Willett WW, Sacks FM. 1999.
Am J Clin Nutr 69(1):30-42

BACKGROUND: The effects of dietary soluble fibers on blood cholesterol are uncertain. OBJECTIVE: This meta-analysis of 67 controlled trials was performed to quantify the cholesterol-lowering effect of major dietary fibers. DESIGN: Least-squares regression analyses were used to test the effect on blood lipids of pectin, oat bran, guar gum, and psyllium. Independent variables were type and amount of soluble fiber, initial cholesterol concentration, and other important study characteristics. RESULTS: Soluble fiber, 2-10 g/d, was associated with small but significant decreases in total cholesterol [-0.045 mmol L(-1).g soluble fiber(-1) (95% CI: -0.054, -0.035)] and LDL cholesterol [-0.057 mmol.L(-1).g(-1) (95% CI: -0.070, -0.044)]. The effects on plasma lipids of soluble fiber from oat, psyllium, or pectin were not significantly different. We were unable to compare effects of guar because of the limited number of studies using 2-10 g/d. Triacylglycerols and HDL cholesterol were not significantly influenced by soluble fiber. Lipid changes were independent of study design, treatment length, and background dietary fat content. CONCLUSIONS: Various soluble fibers reduce total and LDL cholesterol by similar amounts. The effect is small within the practical range of intake. For example, 3 g soluble fiber from oats (3 servings of oatmeal, 28 g each) can decrease total and LDL cholesterol by approximately 0.13 mmol/L. Increasing soluble fiber can make only a small contribution to dietary therapy to lower cholesterol.

Demonstration of rapid onset vascular endothelial dysfunction after hyperhomocysteinemia: an effect reversible with vitamin C therapy.

Chambers JC, McGregor A, Jean-Marie J, Obeid OA, Kooner JS. 1999.
Circulation 99:1156-60

BACKGROUND: Hyperhomocysteinemia is a major and independent risk factor for vascular disease. The mechanisms by which homocysteine promotes atherosclerosis are not well understood. We hypothesized that elevated homocysteine concentrations are associated with rapid onset endothelial dysfunction, which is mediated through oxidant stress mechanisms and can be inhibited by the antioxidant vitamin C. Methods and RESULTS: We studied 17 healthy volunteers (10 male and 7 female) aged 33 (range 21 to 59) years. Brachial artery diameter responses to hyperemic flow (endothelium dependent), and glyceryltrinitrate (GTN, endothelium independent) were measured with high resolution ultrasound at 0 hours (fasting), 2 hours, and 4 hours after (1) oral methionine (L-methionine 100 mg/kg), (2) oral methionine preceded by vitamin C (1g/day, for 1 week), and (3) placebo, on separate days and in random order. Plasma homocysteine increased (0 hours, 12.8+/-1.4; 2 hours, 25.4+/-2.5; and 4 hours, 31. 2+/-3.1 micromol/l, P<0.001), and flow-mediated dilatation fell (0 hours, 4.3+/-0.7; 2 hours, 1.1+/-0.9; and 4 hours, -0.7+/-0.8%) after oral L-methionine. There was an inverse linear relationship between homocysteine concentration and flow-mediated dilatation (P<0. 001). Pretreatment with vitamin C did not affect the rise in homocysteine concentrations after methionine (0 hours, 13.6+/-1.6; 2 hours, 28.3+/-2.9; and 4 hours, 33.8+/-3.7 micromol/l, P=0.27), but did ameliorate the reduction in flow-mediated dilatation (0 hours, 4. 0+/-1.0; 2 hours, 3.5+/-1.2 and 4 hours, 2.8+/-0.7%, P=0.02). GTN-induced endothelium independent brachial artery dilatation was not affected after methionine or methionine preceded by vitamin C. CONCLUSIONS: We conclude that an elevation in homocysteine concentration is associated with an acute impairment of vascular endothelial function that can be prevented by pretreatment with vitamin C in healthy subjects. Our results support the hypothesis that the adverse effects of homocysteine on vascular endothelial cells are mediated through oxidative stress mechanisms.

Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice.

Collaborative Group of the Primary Prevention Project (PPP) 2001.
Lancet 357(9250):89-95

BACKGROUND: In addition to the treatment of specific cardiovascular risk factors, intervention which interferes with the general mechanisms of atherosclerosis could further reduce the incidence of cardiovascular events. We aimed to investigate in general practice the efficacy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with one or more major cardiovascular risk factors. METHODS: We did a randomised controlled open 2x2 factorial trial to investigate low-dose aspirin (100 mg/day) and vitamin E (300 mg/day) in the prevention of cardiovascular events, in people with one or more of the following: hypertension, hypercholesterolaemia, diabetes, obesity, family history of premature myocardial infarction, or individuals who were elderly. FINDINGS: 4495 people (2583 female, mean age 64.4 years) were included in the trial. After a mean follow-up of 3.6 years the trial was prematurely stopped on ethical grounds when newly available evidence from other trials on the benefit of aspirin in primary prevention was strictly consistent with the results of the second planned interim analysis. Aspirin lowered the frequency of all the endpoints, being significant for cardiovascular death (from 1.4 to 0.8%; relative risk 0.56 [95% CI 0.31-0.99]) and total cardiovascular events (from 8.2 to 6.3%; 0.77 [0.62-0.95]). Severe bleedings were more frequent in the aspirin group than the no-aspirin group (1.1% vs 0.3%; p<0.0008). Vitamin E showed no effect on any prespecified endpoint. Analyses were by intention-to-treat. INTERPRETATION: In women and men at risk of having a cardiovascular event because of the presence of at least one major risk factor, low-dose aspirin given in addition to treatment of specific risk factors contributes an additional preventive effect, with an acceptable safety profile. The results on vitamin E's cardiovascular primary preventive efficacy are not conclusive per se, although our results are consistent with the negative results of other large published trials on secondary prevention.

Three months supplementation of hyperhomocysteinaemic patients with folic acid and vitamin B6 improves biological markers of endothelial dysfunction.

Constans J, Blann AD, Resplandy F, Parrot F, Renard M, Seigneur M, Guerin V, BoisseauM, Conri C. 1999. Br J Haematol 107:776-8

Hyperhomocysteinaemia is a risk factor for premature atherosclerosis and venous thromboembolic disease. Supplementation with folic acid and vitamin B6 has been shown to decrease plasma homocysteine but data fail to assess an effect on the progression of vascular disease. We measured plasma homocysteine and two markers of endothelial injury (plasma soluble thrombomodulin and von Willebrand factor) at baseline and after 3 months of treatment with folic acid and vitamin B6. After this treatment there was a significant decrease in fasting soluble thrombomodulin (-15 ng/ml, 95%CI 5-22.2). Von Willebrand factor was significantly raised after methionine load at baseline but did not significantly rise after supplementation.

Alpha tocopherol supplementation decreases serum C-reactive protein and monocyte interleukin-6 levels in normal volunteers and type 2 diabetic patients.

Devaraj S, Jialal I. 2000.
Free Radic Biol Med 29(8):790-2

Type 2 diabetic subjects have an increased propensity to premature atherosclerosis. Alpha tocopherol (AT), a potent antioxidant, has several anti-atherogenic effects. There is scanty data on AT supplementation on inflammation in Type 2 diabetic subjects. The aim of the study was to test the effect of RRR-AT supplementation (1200 IU/d) on plasma C-reactive protein (CRP) and interleukin-6 (IL-6) release from activated monocyte in Type 2 diabetic patients with and without macrovascular complications compared to matched controls. The volunteers comprised Type 2 diabetic subjects with macrovascular disease (DM2-MV, n = 23), Type 2 diabetic subjects without macrovascular complications (DM2, n = 24), and matched controls (C, n = 25). Plasma high sensitive CRP (Hs-CRP) and Monocyte IL-6 were assayed at baseline, following 3 months of supplementation and following a 2 month washout phase. DM2-MV subjects have elevated HsCRP and monocyte IL-6 compared to controls. AT supplementation significantly lowered levels of C-reactive protein and monocyte interleukin-6 in all three groups. In conclusion, AT therapy decreases inflammation in diabetic patients and controls and could be an adjunctive therapy in the prevention of atherosclerosis.

Effect of vitamin C on ambulatory blood pressure and plasma lipids in older persons.

Fotherby MD, Williams JC, Forster LA, Craner P, Ferns GA. 2000.
J Hypertens 18(4):411-415

OBJECTIVES: To determine the effect of oral vitamin C supplements on ambulatory blood pressure and plasma lipids. DESIGN: A 6-month double-blind randomized placebo-controlled cross-over study with a 1 - week washout between cross-over periods. METHODS: Vitamin C 500 mg daily or matching placebo was given to 40 men and women aged between 60 and 80 years for 3 months each in a cross-over fashion. Clinic and 24-h ambulatory blood pressure, plasma ascorbate and lipids were measured at baseline and at the end of each cross-over phase. RESULTS: Clinic blood pressure did not change between placebo and vitamin C phases. Daytime ambulatory blood pressure showed a small but significant fall in systolic blood pressure (2.0 +/- 5.2 mmHg; 95% confidence interval 0-3.9 mmHg) but not in diastolic blood pressure. Regression analysis showed that with increasing baseline daytime blood pressure the fall in blood pressure with vitamin C supplementation increased. Regression analysis of the change in high-density lipoprotein (HDL) cholesterol showed a significant effect of sex on the change in HDL cholesterol. In women, but not men, HDL cholesterol increased significantly by 0.08 +/- 0.11 mmol/l, P=0.007. There was no change in low-density lipoprotein cholesterol between treatment periods. CONCLUSION: In older adults high intakes of ascorbic acid have modest effects on lowering high systolic blood pressure, which could contribute to the reported association between higher vitamin C intake and lower risk of cardiovascular disease and stroke.

Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial.

GISSI-Prevenzione Investigators. 1999.
Lancet 354:447-55

BACKGROUND: There is conflicting evidence on the benefits of foods rich in vitamin E (alpha-tocopherol), n-3 polyunsaturated fatty acids (PUFA), and their pharmacological substitutes. We investigated the effects of these substances as supplements in patients who had myocardial infarction. METHODS: From October, 1993, to September, 1995, 11,324 patients surviving recent (< or = 3 months) myocardial infarction were randomly assigned supplements of n-3 PUFA (1 g daily, n=2836), vitamin E (300 mg daily, n=2830), both (n=2830), or none (control, n=2828) for 3.5 years. The primary combined efficacy endpoint was death, non-fatal myocardial infarction, and stroke. Intention-to-treat analyses were done according to a factorial design (two-way) and by treatment group (four-way). FINDINGS: Treatment with n-3 PUFA, but not vitamin E, significantly lowered the risk of the primary endpoint (relative-risk decrease 10% [95% CI 1-18] by two-way analysis, 15% [2-26] by four-way analysis). Benefit was attributable to a decrease in the risk of death (14% [3-24] two-way, 20% [6-33] four-way) and cardiovascular death (17% [3-29] two-way, 30% [13-44] four-way). The effect of the combined treatment was similar to that for n-3 PUFA for the primary endpoint (14% [1-26]) and for fatal events (20% [5-33]). INTERPRETATION: Dietary supplementation with n-3 PUFA led to a clinically important and statistically significant benefit. Vitamin E had no benefit. Its effects on fatal cardiovascular events require further exploration.

Long-term ascorbic acid administration reverses endothelial vasomotor dysfunction in patients with coronary artery disease.

Gocke N, Keaney JF Jr, Frei B, Holbrook M, Olesiak M, Zachariah BJ, Leeuwenburgh C, Heinecke JW, Vita JA. 1999.
Circulation 99(25):3234-40

BACKGROUND: Loss of endothelium-derived nitric oxide (EDNO) contributes to the clinical expression of coronary artery disease (CAD). Increased oxidative stress has been linked to impaired endothelial vasomotor function in atherosclerosis, and recent studies demonstrated that short-term ascorbic acid treatment improves endothelial function. METHODS AND RESULTS: In a randomized, double-blind, placebo-controlled study, we examined the effects of single-dose (2 g PO) and long-term (500 mg/d) ascorbic acid treatment on EDNO-dependent flow-mediated dilation of the brachial artery in patients with angiographically established CAD. Flow-mediated dilation was examined by high-resolution vascular ultrasound at baseline, 2 hours after the single dose, and 30 days after long-term treatment in 46 patients with CAD. Flow-mediated dilation improved from 6.6+/-3.5% to 10.1+/-5.2% after single-dose treatment, and the effect was sustained after long-term treatment (9. 0+/-3.7%), whereas flow-mediated dilation was 8.6+/-4.7% at baseline and remained unchanged after single-dose (7.8+/-4.4%) and long-term (7.9+/-4.5%) treatment with placebo (P=0.005 by repeated-measures ANOVA). Plasma ascorbic acid concentrations increased from 41.4+/-12. 9 to 115.9+/-34.2 micromol/L after single-dose treatment and to 95. 0+/-36.1 micromol/L after long-term treatment (P<0.001). CONCLUSIONS: In patients with CAD, long-term ascorbic acid treatment has a sustained beneficial effect on EDNO action. Because endothelial dysfunction may contribute to the pathogenesis of cardiovascular events, this study indicates that ascorbic acid treatment may benefit patients with CAD.

Dietary supplementation with marine Omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia.

Goodfellow J, Bellamy MF, Ramsey MW, Jones CJ, Lewis MJ. 2000.
J Am Coll Cardiol 35(2):265-70

OBJECTIVE: This work was undertaken to determine whether dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. BACKGROUND: Marine omega-3 fatty acids improve vascular function, but the underlying mechanism(s) are unclear. We studied the effects of marine omega-3 fatty acids on large artery endothelial function in subjects with hypercholesterolemia. METHODS: Hypercholesterolemic subjects with no other known cause for endothelial dysfunction were recruited to a prospective, placebo-controlled, randomized, double-blind, parallel-group study. Treatment with omega-3 fatty acids at a dose of 4 g/day (n = 15/group) was compared with placebo, at the beginning (day 0) and end (day 120) of a four-month treatment period. Endothelial function was assessed pre- and posttreatment by noninvasive ultrasonic vessel wall tracking of brachial artery flow-mediated dilation (FMD). RESULTS: Treatment with marine omega-3 fatty acids resulted in a significant improvement in FMD (0.05 +/- 0.12 to 0.12 +/- 0.07 mm, $p < 0.05$) and a significant reduction in triglycerides (2.07 +/- 1.13 to 1.73 +/- 0.95 mmol/liter, $p < 0.05$), whereas treatment with placebo resulted in no change in FMD (0.03 +/- 0.10 to 0.04 +/- 0.10 mm) or triglycerides (2.29 +/- 2.09 to 2.05 +/- 1.36 mmol/liter) (both $p < 0.05$ treated compared with control). Responses to sublingual glyceryl trinitrate were unchanged. CONCLUSIONS: Marine omega-3 fatty acids improve large artery endothelium-dependent dilation in subjects with hypercholesterolemia without affecting endothelium-independent dilation.

Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease.

Hennekens CH, Buring JE, Manson JE, Stampfer M, Rosner B, Cook NR, Belanger C, LaMotte F, Gaziano JM, Ridker PM, Willett W, Peto R. 1996.
N Engl J Med. 334(18):1145-9

BACKGROUND. Observational studies suggest that people who consume more fruits and vegetables containing beta carotene have somewhat lower risks of cancer and cardiovascular disease, and earlier basic research suggested plausible mechanisms. Because large randomized trials of long duration were necessary to test this hypothesis directly, we conducted a trial of beta carotene supplementation. METHODS. In a randomized, double-blind, placebo-controlled trial of beta carotene (50 mg on alternate days), we enrolled 22,071 male physicians, 40 to 84 years of age, in the United States; 11 percent were current smokers and 39 percent were former smokers at the beginning of the study in 1982. By December 31, 1995, the scheduled end of the study, fewer than 1 percent had been lost to follow-up, and compliance was 78 percent in the group that received beta carotene. RESULTS. Among 11,036 physicians randomly assigned to receive beta carotene and 11,035 assigned to receive placebo, there were virtually no early or late differences in the overall incidence of malignant neoplasms or cardiovascular disease, or in overall mortality. In the beta carotene group, 1273 men had any malignant neoplasm (except nonmelanoma skin cancer), as compared with 1293 in the placebo group (relative risk, 0.98; 95 percent confidence interval, 0.91 to 1.06). There were also no significant differences in the number of cases of lung cancer (82 in the beta carotene group vs. 88 in the placebo group); the number of deaths from cancer (386 vs. 380), deaths from any cause (979 vs. 968), or deaths from cardiovascular disease (338 vs. 313); the number of men with myocardial infarction (468 vs. 489); the number with stroke (367 vs. 382); or the number with any one of the previous three end points (967 vs. 972). Among current and former smokers, there were also no significant early or late differences in any of these end points. CONCLUSIONS. In this trial among healthy men, 12 years of supplementation with beta carotene produced neither benefit nor harm in terms of the incidence of malignant neoplasms, cardiovascular disease, or death from all causes.

Serial coronary angiographic evidence that antioxidant vitamin intake reduces progression of coronary artery atherosclerosis.

Hodis HN, Mack WJ, LaBree L, Cashin-Hemphill L, Sevanian A, Johnson R, Azen SP. 1995.
JAMA 273(23):1849-54

OBJECTIVE--To explore the association of supplementary and dietary vitamin E and C intake with the progression of coronary artery disease. DESIGN--A subgroup analysis of the on-trial antioxidant vitamin intake database acquired in the Cholesterol Lowering Atherosclerosis Study, a randomized, placebo-controlled, serial angiographic clinical trial evaluating the risk and benefit of colestipol-niacin on coronary artery disease progression. SETTING--Community- and university-based cardiac catheterization laboratories. SUBJECTS--A total of 156 men aged 40 to 59 years with previous coronary artery bypass graft surgery. INTERVENTION--Supplementary and dietary vitamin E and C intake (nonrandomized) in association with cholesterol-lowering diet and either colestipol-niacin or placebo (randomized). OUTCOME--Change per subject in the percentage of vessel diameter obstructed because of stenosis (%S) determined by quantitative coronary angiography after 2 years of randomized therapy on all lesions, mild/moderate lesions (< 50%S), and severe lesions (> or = 50%S). RESULTS--Overall, subjects with supplementary vitamin E intake of 100 IU per day or greater demonstrated less coronary artery lesion progression than did subjects with supplementary vitamin E intake less than 100 IU per day for all lesions (P = .04) and for mild/moderate lesions (P = .01). Within the drug group, benefit of supplementary vitamin E intake was found for all lesions (P = .02) and mild/moderate lesions (P = .01). Within the placebo group, benefit of supplementary vitamin E intake was not found. No benefit was found for use of supplementary vitamin C exclusively or in conjunction with supplementary vitamin E, use of multivitamins, or increased dietary intake of vitamin E or vitamin C. CONCLUSIONS--These results indicate an association between supplementary vitamin E intake and angiographically demonstrated reduction in coronary artery lesion progression. Verification from carefully designed, randomized, serial arterial imaging end point trials is needed.

Vitamin C improves endothelial function of conduit arteries in patients with chronic heart failure.

Hornig B, Arakawa N, Kohler C, Drexler H. 1998.
Circulation 97:363-8

BACKGROUND: Chronic heart failure (CHF) is associated with endothelial dysfunction including impaired endothelium-mediated, flow-dependent dilation (FDD). There is evidence for increased radical formation in CHF, raising the possibility that nitric oxide is inactivated by radicals, thereby impairing endothelial function. To test this hypothesis, we determined the effect of the antioxidant vitamin C on FDD in patients with CHF. METHODS AND RESULTS: High-resolution ultrasound and Doppler was used to measure radial artery diameter and blood flow in 15 patients with CHF and 8 healthy volunteers. Vascular effects of vitamin C (25 mg/min IA) and placebo were determined at rest and during reactive hyperemia (causing endothelium-mediated dilation) before and after intra-arterial infusion of N-monomethyl-L-arginine (L-NMMA) to inhibit endothelial synthesis of nitric oxide. Vitamin C restored FDD in patients with heart failure after acute intra-arterial administration (13.2+/-1.7% versus 8.2+/-1.0%; P<.01) and after 4 weeks of oral therapy (11.9+/-0.9% versus 8.2+/-1.0%; P<.05). In particular, the portion of FDD mediated by nitric oxide (ie, inhibited by L-NMMA) was increased after acute as well as after chronic treatment (CHF baseline: 4.2+/-0.7%; acute: 9.1+/-1.3%; chronic: 7.3+/-1.2%; normal subjects: 8.9+/-0.8%; P<.01). CONCLUSIONS: Vitamin C improves FDD in patients with CHF as the result of increased availability of nitric oxide. This observation supports the concept that endothelial dysfunction in patients with CHF is, at least in part, due to accelerated degradation of nitric oxide by radicals.

The effect of modest vitamin E supplementation on lipid peroxidation products and other cardiovascular risk factors in diabetic patients.

Jain SK, McVie R, Jaramillo JJ, Palmer M, Smith T, Meachum ZD, Little RL. 1996.
Lipids Suppl:S87-90

Among many factors, elevated lipids and lipid peroxide levels in blood are major risk factors in the development of cardiovascular disease in diabetic patients. This study has examined whether oral supplementation of vitamin E, an antioxidant, has any effect on blood lipid peroxidation products (LP) and lipid profile of diabetic patients. Thirty-five diabetics (D) were supplemented with DL-alpha-tocopherol (E) capsule (orally, 100 IU/d) or placebo (P) for three months in double-blind clinical trials. Plasma E was analyzed by HPLC and LP by the thiobarbituric acid-reactivity; serum lipids by auto-analyzer. Data were analyzed using paired t-test and Wilcoxon Signed Rank Test. Vitamin E supplementation significantly lowered LP and lipid levels in diabetic patients; there were no differences in these parameters after P supplementation. There were no differences in the duration of diabetes and ages of D between P- and E- supplemented groups. This study suggests that vitamin E supplementation significantly lowers blood LP and lipid levels in diabetic patients.

The effect of supplementation with omega-3 fatty acids on soluble markers of endothelial function in patients with coronary heart disease.

Johansen O, Seljflot I, Hostmark AT, Arnesen H. 1999.
Arterioscler Thromb Vasc Biol 19:1681-6

During progression of atherosclerosis the overlying endothelial cells alter their expression of some surface molecules. Circulating levels of such molecules may be quantified. We investigated the effect of omega-3 fatty acids (n-3 FA) on the levels of tissue plasminogen activator antigen, von Willebrand factor, and the soluble forms of thrombomodulin, P-selectin, E-selectin, and vascular cell adhesion molecule-1 in 54 patients with coronary heart disease. Twenty-three of the patients had taken 5.1 g/d n-3 FA for 6 months (group I) and 31 were given corn oil as placebo (group II). For another 4 weeks ("the study period") they all got 5.1 g/d of n-3 FA. Compliance was confirmed by demonstration of changes in relevant fatty acids in serum phospholipids. At baseline, significant differences between the groups were found with lower median values of von Willebrand factor (128% versus 147%) and soluble thrombomodulin (24.9 versus 32.5 ng/mL) and higher median values of soluble E-selectin (41.4 versus 35.5 ng/mL) and soluble vascular cell adhesion molecule-1 (573 versus 473 ng/mL) in group I. During the study period differences in changes between the groups were found; tissue plasminogen activator antigen and soluble thrombomodulin decreased (P for difference between the groups 0.001 and 0.015, respectively), whereas soluble E-selectin and soluble vascular cell adhesion molecule-1 increased (P for difference between the groups <0.01 for both) in group II relative to group I. Our results indicate that n-3 FA supplementation decreases hemostatic markers of atherosclerosis, whereas markers of inflammation may be increased. The latter may be the result of lipid peroxidation as a simultaneous decrease of vitamin E and increase in thiobarbituric acid-reactive substances were observed.

Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women.

Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. 1996.
N Engl J Med 334(18):1156-62

BACKGROUND: The role of dietary antioxidant vitamins in preventing coronary heart disease has aroused considerable interest because of the knowledge that oxidative modification of low-density lipoprotein may promote atherosclerosis. METHODS. We studied 34,486 postmenopausal women with no cardiovascular disease who in early 1986 completed a questionnaire that assessed, among other factors, their intake of vitamins A, E, and C from food sources and supplements. During approximately seven years of follow-up (ending December 31, 1992), 242 of the women died of coronary heart disease. RESULTS. In analyses adjusted for age and dietary energy intake, vitamin E consumption appeared to be inversely associated with the risk of death from coronary heart disease. This association was particularly striking in the subgroup of 21,809 women who did not consume vitamin supplements (relative risks from lowest to highest quintile of vitamin E intake, 1.0, 0.68, 0.71, 0.42, and 0.42; P for trend 0.008). After adjustment for possible confounding variables, this inverse association remained (relative risks from lowest to highest quintile, 1.0, 0.70, 0.76, 0.32, and 0.38; P for trend, 0.004). There was little evidence that the intake of vitamin E from supplements was associated with a decreased risk of death from coronary heart disease, but the effects of high-dose supplementation and the duration of supplement use could not be definitely addressed. Intake of vitamins A and C did not appear to be associated with the risk of death from coronary heart disease. CONCLUSIONS. These results suggest that in postmenopausal women the intake of vitamin E from food is inversely associated with the risk of death from coronary heart disease and that such women can lower their risk without using vitamin supplements. By contrast, the intake of vitamins A and C was not associated with lower risks of dying from coronary disease.

Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study.

Lee IM, Cook NR, Manson JE, Buring JE, Hennekens CH. 1999.
J Natl Cancer Inst. 91(24):2102-6

BACKGROUND: In observational studies, individuals with high intakes of fruits and vegetables containing beta-carotene experience lower risks of developing cancer. However, the few randomized trials of beta-carotene supplementation show no overall benefits; some even suggest harm. This trial was designed to test the effects of beta-carotene supplementation in women. METHODS: The Women's Health Study is a randomized, double-blind, placebo-controlled trial originally testing aspirin, vitamin E, and beta-carotene in the prevention of cancer and cardiovascular disease among 39 876 women aged 45 years or older. The beta-carotene component was terminated early after a median treatment duration of 2.1 years (range = 0.00-2. 72 years). Statistical tests were two-sided. RESULTS: Among women randomly assigned to receive beta-carotene (50 mg on alternate days; n = 19 939) or placebo (n =19 937), there were no statistically significant differences in incidence of cancer, cardiovascular disease, or total mortality after a median of 4.1 years (2.1 years' treatment plus another 2.0 years' follow-up). There were 378 cancers in the beta-carotene group and 369 cancers in the placebo group (relative risk [RR] = 1.03; 95% confidence interval [CI] = 0.89-1. 18). There were no statistically significant differences for any site-specific cancer or during years 1 and 2 combined and years 3 and up combined. For cardiovascular disease, there were no statistically significant differences for myocardial infarction (42 in the beta-carotene group versus 50 in the placebo group), stroke (61 versus 43), deaths from cardiovascular causes (14 versus 12), or the combined end point of these three events (116 versus 102; among women with more than one event, only the first was counted). Deaths from any cause were similar in the two groups (59 versus 55). Among smokers at baseline (13% of all women), there were no statistically significant differences in overall incidence of cancer (RR = 1.11; 95% CI = 0.78-1.58) or cardiovascular disease (RR = 1.01; 95% CI = 0. 62-1.63). CONCLUSION: Among apparently healthy women, there was no benefit or harm from beta-carotene supplementation for a limited period on the incidence of cancer and of cardiovascular disease.

Ascorbic acid reverses endothelial vasomotor dysfunction in patients with coronary artery disease.

Levine GN, Frei B, Koulouris SN, Gerhard MD, Keaney JF, Vita JA. 1996.
Circulation 93(6):1107-13

BACKGROUND: In the setting of atherosclerosis, endothelial vasomotor function is abnormal. Increased oxidative stress has been implicated as one potential mechanism for this observation. We therefore hypothesized that an antioxidant, ascorbic acid, would improve endothelium-dependent arterial dilation in patients with coronary artery disease. METHODS AND RESULTS: Brachial artery endothelium-dependent dilation in response to hyperemia was assessed by high-resolution vascular ultrasound before and 2 hours after oral administration of either 2 g ascorbic acid or placebo in a total of 46 patients with documented coronary artery disease. Plasma ascorbic acid concentration increased 2.5-fold 2 hours after treatment (46+/-8 to 114+/-11 micromol/L, P=.001). In the prospectively defined group of patients with an abnormal baseline response (<5% dilation), ascorbic acid produced marked improvement in dilation (2.0+/-0.6% to 9.7+/-2.0%), whereas placebo had no effect (1.1+/-1.5% to 1.7+/-1.5%, P=.003 for ascorbic acid versus placebo). Ascorbic acid had no effect on hyperemic flow or arterial dilation to sublingual nitroglycerin. CONCLUSIONS: Ascorbic acid reverses endothelial vasomotor dysfunction in the brachial circulation of patients with coronary artery disease. These findings suggest that increased oxidative stress contributes to endothelial dysfunction in patients with atherosclerosis and that endothelial dysfunction may respond to antioxidant therapy.

Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the established populations for epidemiologic studies of the elderly.

Losonczy KG, Harris TB, Havlik RJ. 1996.
Am J Clin Nutr 64(2):190-6

We examined vitamin E and vitamin C supplement use in relation to mortality risk and whether vitamin C enhanced the effects of vitamin E in 11,178 persons aged 67-105 y who participated in the Established Populations for Epidemiologic Studies of the Elderly in 1984-1993. Participants were asked to report all nonprescription drugs currently used, including vitamin supplements. Persons were defined as users of these supplements if they reported individual vitamin E and/or vitamin C use, not part of a multivitamin. During the follow-up period there were 3490 deaths. Use of vitamin E reduced the risk of all-cause mortality [relative risk (RR) = 0.66; 95% CI: 0.53, 0.83] and risk of coronary disease mortality (RR = 0.53; 95% CI: 0.34, 0.84). Use of vitamin E at two points in time was also associated with reduced risk of total mortality compared with that in persons who did not use any vitamin supplements. Effects were strongest for coronary heart disease mortality (RR = 0.37; 95% CI: 0.15, 0.90). The RR for cancer mortality was 0.41 (95% CI: 0.15, 1.08). Simultaneous use of vitamins E and C was associated with a lower risk of total mortality (RR = 0.58; 95% CI: 0.42, 0.79) and coronary mortality (RR = 0.47; 95% CI: 0.25, 0.87). Adjustment for alcohol use, smoking history, aspirin use, and medical conditions did not substantially alter these findings. These findings are consistent with those for younger persons and suggest protective effects of vitamin E supplements in the elderly.

Lower ischemic heart disease incidence and mortality among vitamin supplement users.

Meyer F, Bairati I, Dagenais GR. 1996.
Can J Cardiol 12(10):930-4

OBJECTIVE: This study assessed the relationship between vitamin supplement use and the occurrence of ischemic heart disease (IHD). DESIGN: A cohort study was conducted between 1985 and 1991 in Quebec City. In 1985, 2313 men provided baseline information on vitamin supplement use and IHD risk factors. Incidence of IHD events was ascertained over the first five years of follow-up. Cox regression models were used to assess the relation between vitamin supplement use and occurrence of IHD events while controlling for confounders. MAIN RESULTS: Vitamin supplement use was consistently associated with a lower incidence of IHD. The adjusted rate ratios and their 95% confidence intervals were: 0.31 (0.09-0.99) for IHD death, 0.53 (0.24-1.11) for MI, 0.76 (0.44-1.65) for angina and 0.73 (0.44-1.22) for a first IHD event. The associations were stronger for IHD death and myocardial infarction, two events assessed with high validity. The inverse association with IHD was more consistent for vitamin E than for any other vitamin. CONCLUSION: This study suggests that the inverse association between vitamin supplement use and IHD is real. The causal nature of the association can only be demonstrated in the context of a randomised intervention trial such as the HOPE study.

Endothelial dysfunction occurs in children with two genetic hyperlipidemias: improvement with antioxidant vitamin therapy.

Mietus-Snyder M, Malloy MJ. 1998.
J Pediatr 133(1):35-40

OBJECTIVE: To measure endothelium-dependent vascular relaxation in children with two genetic hyperlipidemias and to assess the effect of antioxidant vitamins on endothelial dysfunction. STUDY DESIGN: Vascular reactivity in the brachial artery was measured in 45 individuals between 6 and 21 years of age (18 with familial hypercholesterolemia [FH], 15 with familial combined hyperlipoproteinemia [FCH], 12 control subjects) with the use of high-resolution two-dimensional ultrasonography. Follow-up studies were done for 11 children after 6 weeks of treatment with tocopherol (400 IU twice a day) and ascorbic acid (500 mg twice a day). RESULTS: The mean percent change in diameter during reactive hyperemia was 2.1 +/- 2.2 (SD) and 2.7 +/- 4.4, in FH and FCH, respectively, compared with 12. +/- 4.9 among control subjects ($p < 0.001$ in each case). The mean percent dilation was significantly increased (2.8 +/- 1.6 to 9.1 +/- 2.3) ($p < 0.001$) after antioxidant therapy. CONCLUSIONS: Impaired endothelium-dependent vasoregulation occurs in children with FCH as well as in those with FH. The improvement in vascular reactivity observed during supplementation with antioxidant vitamins suggests that reactive oxygen species derived from oxidized lipoproteins may be responsible for the impairment of vasoregulation in subjects with hyperlipidemia.

Antioxidant nutrient supplementation reduces the susceptibility of low density lipoprotein to oxidation in patients with coronary artery disease.

Mosca L, Rubenfire M, Mandel C, Rock C, Tarshis T, Tsai A, Pearson T. 1997.
J Am Coll Cardiol 30(2):392-9

OBJECTIVE: This study sought to determine the effect of antioxidant supplementation on the susceptibility of low density lipoprotein (LDL) to oxidation in patients with established cardiovascular disease (CVD). BACKGROUND: Data are inconsistent regarding the role of antioxidant nutrients in the prevention of CVD. METHODS: The study design was a 12-week, double-blind, placebo-controlled clinical trial. Patients with CVD ($n = 45$) were randomized to 1) placebo control; 2) 400 IU of vitamin E, 500 mg of vitamin C, 12 mg of beta-carotene (mid-dose); or 3) 800 IU of vitamin E, 1,000 mg of vitamin C, 24 mg of beta-carotene (high dose) daily. Reduced susceptibility of LDL to oxidation was estimated by an increase in lag phase (minutes). Baseline and 6- and 12-week measurements of lipoproteins and lag phase were obtained. Plasma levels of antioxidants were measured at baseline and 12 weeks. RESULTS: Concentrations of alpha-tocopherol, vitamin C and beta-carotene significantly increased in the mid- and high dose groups during the trial. Lag phase significantly increased from baseline (190.1 +/- 63.8 min [mean +/- SD]) to 12 weeks (391.1 +/- 153.0 min) in the high dose group ($p < 0.01$). A nonsignificant increase in lag phase in the mid-dose group was observed during the same time interval. A dose response was found for mean percent change from baseline to 12 weeks for lag phase for the placebo, mid- and high dose groups ($p = 0.004$ for trend). CONCLUSIONS: A high dose combination of antioxidant nutrients reduces the susceptibility of LDL to oxidation in patients with CVD and may be useful in secondary prevention.

Vitamin E improves arterial compliance in middle-aged men and women.

Mottram P, Shige H, Nestel P. 1999.
Atherosclerosis 145(2):399-404

Diminished arterial compliance, or loss of elasticity in large arteries, is an emerging cardiovascular risk factor with a reversible component that includes improved endothelial function. Vitamin E, which may reduce cardiovascular risk, can lower vascular resistance. Twenty-eight middle-aged men and women were randomized through a double-blind design to 8 weeks of supplemental vitamin E (400 IU daily) or placebo. Compliance was determined non-invasively from simultaneous measurements of aortic flow and carotid pressure at baseline and after 4 and 8 weeks. RESULTS: arterial compliance increased by 37% at 4 weeks and by 44% at 8 weeks ($P = 0.01$) only in the vitamin E group and was independent of an effect on arterial pressure. A rise was seen in 12/14 subjects. There was no significant change with placebo (+ 8%). CONCLUSIONS: short-term vitamin E supplementation improves arterial compliance.

A randomized, single-blind, placebo-controlled trial of the effects of 200 mg alpha-tocopherol on the oxidation resistance of atherogenic lipoproteins.

Porkkala-Sarataho EK, Nyyssonen MK, Kaikkonen JE, Poulsen HE, Hayn EM, Salonen RM, Salonen JT. 1998.
Am J Clin Nutr 68(5):1034-41

Supplementation with high doses of alpha-tocopherol has increased the oxidation resistance of LDL in many clinical trials. There have been only a few placebo-controlled trials in healthy persons of alpha-tocopherol doses usually contained in dietary supplements. We carried out a single-blind, placebo-controlled, randomized trial to examine the effect of 200 mg RRR-alpha-tocopheryl acetate/d on the oxidation resistance of atherogenic lipoproteins (VLDL+LDL including intermediate-density lipoproteins) in 40 smoking men. VLDL+LDL oxidation resistance was assessed as conjugated dienes after copper induction and hemin degradation after hydrogen peroxide induction. Also, the LDL total peroxyl-radical trapping antioxidant parameter (LDL TRAP) and plasma malondialdehyde were measured at baseline and after 2 mo of supplementation. Plasma RRR-alpha-tocopherol concentrations were measured at 2-h intervals for 12 h at baseline and after 2 mo of supplementation. Compared with placebo, 200-mg RRR-alpha-tocopheryl acetate supplementation elevated plasma and VLDL+LDL alpha-tocopherol concentrations, LDL TRAP, and oxidation resistance of VLDL+LDL. Plasma alpha-tocopherol increased by 88% ($P < 0.0001$), VLDL+LDL alpha-tocopherol increased by 90% ($P < 0.0001$), and LDL TRAP by 58% ($P < 0.0001$). The time to the start of oxidation (lag time) was prolonged by 34% when assessed with a copper-induced method and by 109% when assessed with a hemin + hydrogen peroxide-induced method; the time to maximal oxidation was prolonged by 21% (copper-induced method) in the vitamin E-supplemented group. Changes in plasma alpha-tocopherol, lipid-standardized alpha-tocopherol, and VLDL+LDL alpha-tocopherol correlated significantly with changes in LDL TRAP, lag time, and time to maximal oxidation. Differences in changes between groups in the area under the curve for plasma alpha-tocopherol were significant ($P < 0.009$). Our results suggest that 200 mg oral RRR-alpha-tocopheryl acetate/d had a clear effect on the in vitro oxidation of VLDL+LDL in smoking men.

Vitamin E consumption and the risk of coronary heart disease in men.

Rimm EB, Stampfer MJ, Ascherio A, Giovannucci E, Colditz GA, Willett WC. 1993.
N Engl J Med 328(20):1450-6

BACKGROUND. The oxidative modification of low-density lipoproteins increases their incorporation into the arterial intima, an essential step in atherogenesis. Although dietary antioxidants, such as vitamin C, carotene, and vitamin E, have been hypothesized to prevent coronary heart disease, prospective epidemiologic data are sparse. METHODS. In 1986, 39,910 U.S. male health professionals 40 to 75 years of age who were free of diagnosed coronary heart disease, diabetes, and hypercholesterolemia completed detailed dietary questionnaires that assessed their usual intake of vitamin C, carotene, and vitamin E in addition to other nutrients. During four years of follow-up, we documented 667 cases of coronary disease. RESULTS. After controlling for age and several coronary risk factors, we observed a lower risk of coronary disease among men with higher intakes of vitamin E (P for trend = 0.003). For men consuming more than 60 IU per day of vitamin E, the multivariate relative risk was 0.64 (95 percent confidence interval, 0.49 to 0.83) as compared with those consuming less than 7.5 IU per day. As compared with men who did not take vitamin E supplements, men who took at least 100 IU per day for at least two years had a multivariate relative risk of coronary disease of 0.63 (95 percent confidence interval, 0.47 to 0.84). Carotene intake was not associated with a lower risk of coronary disease among those who had never smoked, but it was inversely associated with the risk among current smokers (relative risk, 0.30; 95 percent confidence interval, 0.11 to 0.82) and former smokers (relative risk, 0.60; 95 percent confidence interval, 0.38 to 0.94). In contrast, a high intake of vitamin C was not associated with a lower risk of coronary disease. CONCLUSIONS. These data do not prove a causal relation, but they provide evidence of an association between a high intake of vitamin E and a lower risk of coronary heart disease in men. Public policy recommendations with regard to the use of vitamin E supplements should await the results of additional studies.

Vitamin E consumption and the risk of coronary disease in women.

Stampfer MJ, Hennekens CH, Manson JE, Colditz GA, Rosner B, Willett WC. 1993.
N Engl J Med 328(20):1444-9

BACKGROUND. Interest in the antioxidant vitamin E as a possible protective nutrient against coronary disease has intensified with the recognition that oxidized low-density lipoprotein may be involved in atherogenesis. METHODS. In 1980, 87,245 female nurses 34 to 59 years of age who were free of diagnosed cardiovascular disease and cancer completed dietary questionnaires that assessed their consumption of a wide range of nutrients, including vitamin E. During follow-up of up to eight years (679,485 person-years) that was 97 percent complete, we documented 552 cases of major coronary disease (437 nonfatal myocardial infarctions and 115 deaths due to coronary disease). RESULTS. As compared with women in the lowest fifth of the cohort with respect to vitamin E intake, those in the top fifth had a relative risk of major coronary disease of 0.66 (95 percent confidence interval, 0.50 to 0.87) after adjustment for age and smoking. Further adjustment for a variety of other coronary risk factors and nutrients, including other antioxidants, had little effect on the results. Most of the variability in intake and reduction in risk was attributable to vitamin E consumed as supplements. Women who took vitamin E supplements for short periods had little apparent benefit, but those who took them for more than two years had a relative risk of major coronary disease of 0.59 (95 percent confidence interval, 0.38 to 0.91) after adjustment for age, smoking status, risk factors for coronary disease, and use of other antioxidant nutrients (including multi-vitamins). CONCLUSIONS. Although these prospective data do not prove a cause-and-effect relation, they suggest that among middle-aged women the use of vitamin E supplements is associated with a reduced risk of coronary heart disease. Randomized trials of vitamin E in the primary and secondary prevention of coronary disease are being conducted; public policy recommendations about the widespread use of vitamin E should await the results of these trials.

Epidemiologic evidence for vitamin E in prevention of cardiovascular disease.

Stampfer MJ, Rimm EB. 1995.
Am J Clin Nutr 62(6 Suppl):1365S-1369S

Ecologic studies of vitamin E have shown that regions with relatively low dietary vitamin E tend to have higher rates of coronary heart disease (CHD), but it is difficult to adjust for other risk factors. Cross-sectional studies in individuals have yielded conflicting results, as have prospective studies based on stored blood samples. Two large prospective studies found that persons who had used vitamin E supplements for > or = 2 y had approximately 40% lower rates of CHD. Short durations and doses of < 100 IU/d had no significant effect. The effect of dietary vitamin E was modest and nonsignificant. Adjustment for a wide array of other coronary risk factors had little effect on the findings, which were specific for vitamin E and not other supplements. The only large, randomized trial found no material reduction in CHD risk for 50 IU vitamin E/d. The epidemiologic evidence suggests that high doses of vitamin E may reduce the risk of CHD.

Vitamin E plus aspirin compared with aspirin alone in patients with transient ischemic attacks.

Steiner M, Glantz M, Lekos A. 1995.
Am J Clin Nutr 62(suppl):1381S-4S

One hundred patients with transient ischemic attacks, minor strokes, or residual ischemic neurologic deficits were enrolled in a double-blind, randomized study comparing the effects of aspirin plus vitamin E [0.4 g (400 IU)/d; n = 52] with aspirin alone (325 mg; n = 48). The patients received study medication for 2 y or until they reached a termination point. Preliminary results show a significant reduction in the incidence of ischemic events in patients in the vitamin E plus aspirin group compared with patients taking only aspirin. There was no significant difference in the incidence of hemorrhagic stroke although both patients who developed it were taking vitamin E. Platelet adhesion was also measured in a randomized subgroup of both study populations by using collagen III as the adhesive surface. There was a highly significant reduction in platelet adhesiveness in patients who were taking vitamin E plus aspirin compared with those taking aspirin only. Measurement of alpha-tocopherol concentrations confirmed compliance of the patients with the medication schedule, showing a near doubling of serum concentrations of alpha-tocopherol. We concluded that the combination of vitamin E and a platelet antiaggregating agent (eg, aspirin) significantly enhances the efficacy of the preventive treatment regimen in patients with transient ischemic attacks and other ischemic cerebrovascular problems.

Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study.

Stephens NG, Parsons A, Schofield PM, Kelly F, Cheeseman K, Mitchinson MJ. 1996.
Lancet 347(9004):781-6

BACKGROUND: Vitamin E (alpha-tocopherol) is thought to have a role in prevention of atherosclerosis, through inhibition of oxidation of low-density lipoprotein. Some epidemiological studies have shown an association between high dietary intake or high serum concentrations of alpha-tocopherol and lower rates of ischaemic heart disease. We tested the hypothesis that treatment with a high dose of alpha-tocopherol would reduce subsequent risk of myocardial infarction (MI) and cardiovascular death in patients with established ischaemic heart disease. METHODS: In this double-blind, placebo-controlled study with stratified randomisation, 2002 patients with angiographically proven coronary atherosclerosis were enrolled and followed up for a median of 510 days (range 3-981). 1035 patients were assigned alpha-tocopherol (capsules containing 800 IU daily for first 546 patients; 400 IU daily for remainder); 967 received identical placebo capsules. The primary endpoints were a combination of cardiovascular death and non-fatal MI as well as non-fatal MI alone. FINDINGS: Plasma alpha-tocopherol concentrations (measured in subsets of patients) rose in the actively treated group (from baseline mean 34.2 micromol/L to 51.1 micromol/L with 400 IU daily and 64.5 micromol/L with 800 IU daily) but did not change in the placebo group. Alpha-tocopherol treatment significantly reduced the risk of the primary trial endpoint of cardiovascular death and non-fatal MI (41 vs 64 events; relative risk 0.53 [95% Cl 0.34-0.83; p=0.005). The beneficial effects on this composite endpoint were due to a significant reduction in the risk of non-fatal MI (14 vs 41; 0.23 [0.11-0.47]; p=0.005); however, there was a non-significant excess of cardiovascular deaths in the alpha-tocopherol group (27 vs 23; 1.18 [0.62-2.27]; p=0.61). All-cause mortality was 36 of 1035 alpha-tocopherol-treated patients and 27 of 967 placebo recipients. INTERPRETATION: We conclude that in patients with angiographically proven symptomatic coronary atherosclerosis, alpha-tocopherol treatment substantially reduces the rate of non-fatal MI, with beneficial effects apparent after 1 year of treatment. The effect of alpha-tocopherol treatment on cardiovascular deaths requires further study.

Combined vitamin B6 plus folic acid therapy in young patients with arteriosclerosis and hyperhomocysteinemia.

Van den Berg M, Franken DG, Boers GH, Blom HJ, Jakobs C, Stehouwer CD, Rauwerda JA. 1994.
J Vasc Surg 20(6):933-40

PURPOSE: Hyperhomocysteinemia is associated with arteriosclerotic and thromboembolic events. The homocysteine-lowering effect of combined treatment with vitamin B6 plus folic acid has never been explored in a large group of patients with vascular disease. Therefore we studied the effects of at least 6 weeks treatment with these vitamins in 72 patients with cardiovascular disease and mild hyperhomocysteinemia (defined as an increase of the plasma homocysteine level after methionine loading greater than 97.5 percentile of age-matched control subjects but less than 200 mumol/L). METHODS: The existence of mild hyperhomocysteinemia was investigated in 309 consecutive patients under 50 years of age with peripheral arterial occlusive disease, cerebral arterial occlusive disease, or coronary artery occlusive disease. All patients with an abnormal loading test result were treated with vitamin B6, 250 mg daily, plus folic acid, 5 mg daily. After 6 weeks of treatment a second methionine loading test was performed to assess the homocysteine-lowering effect. RESULTS: Mild hyperhomocysteinemia was detected in 72 patients (23%), 33 (46%) of whom also had hyperhomocysteinemia when fasting. Treatment with vitamin B6 plus folic acid normalized the postload plasma homocysteine concentration in 66 of the 72 patients (92%), whereas fasting hyperhomocysteinemia was normalized in 30 of 33 (91%) patients. In six patients therapy failed to achieve normalization of the postload homocysteine levels. In three of these patients, the same treatment was continued for an additional 6 weeks, and in the remaining three patients betaine was added to the treatment regimen. After 6 weeks of additional treatment all six patients had normal postload plasma homocysteine concentrations. CONCLUSION: The prevalence of mild hyperhomocysteinemia in young patients with arterial occlusive disease is high. Simple and inexpensive therapy with vitamin B6 plus folic acid will normalize homocysteine metabolism, as assessed by the homocysteine plasma level after methionine loading, in virtually all these patients.

Effect of homocysteine-lowering treatment with folic acid plus vitamin B6 on progression of subclinical atherosclerosis: a randomised, placebo-controlled trial.

Vermeulen EG, Stehouwer CD, Twisk JW, van den Berg M, de Jong SC, Mackaay AJ, van Campen CM, Visser FC, Jakobs CA, Bulterjis EJ, Rauwerda JA. 2000.
Lancet 355(9203):517-22

BACKGROUND: A high plasma homocysteine concentration is associated with increased risk of atherothrombotic disease. We investigated the effects of homocysteine-lowering treatment (folic acid plus vitamin B6) on markers of subclinical atherosclerosis among healthy siblings of patients with premature atherothrombotic disease. METHODS: We did a randomised, placebo-controlled trial among 158 healthy siblings of 167 patients with premature atherothrombotic disease. 80 were assigned placebo and 78 were assigned 5 mg folic acid and 250 mg vitamin B6 daily for 2 years. The primary endpoint was the development or progression of subclinical atherosclerosis as estimated from exercise electrocardiography, the ankle-brachial pressure index, and carotid and femoral ultrasonography. FINDINGS: Ten participants in the treatment group, and 14 in the placebo group dropped out. Vitamin treatment, compared with placebo, was associated with a decrease in fasting homocysteine concentration (from 14.7 to 7.4 micromol/L vs from 14.7 to 12.0 micromol/L), and in postmethionine homocysteine concentration (from 64.9 to 34.9 micromol/L vs from 64.8 to 50.3 micromol/L). It was also associated with a decreased rate of abnormal exercise electrocardiography tests (odds ratio 0.40 [0.17-0.93]; p=0.035). There was no apparent effect of vitamin treatment on ankle-brachial pressure indices (0.87 [0.56-1.33]), or on carotid and peripheral-arterial outcome variables (1.02 [0.26-4.05] and 0.86 [0.47-1.59], respectively). INTERPRETATION: Homocysteine-lowering treatment with folic acid plus vitamin B6 in healthy siblings of patients with premature atherothrombotic disease is associated with a decreased occurrence of abnormal exercise electrocardiography tests, which is consistent with a decreased risk of atherosclerotic coronary events.

Effect of B-group vitamins and antioxidant vitamins on hyperhomocysteinemia: a double-blind, randomized, factorial-design, controlled trial.

Woodside JV, Yarnell JW, McMaster D, Young IS, Harmon DL, McCrum EE, Patterson CC, Gey KF, Whitehead AS, Evans A. 1998.
Am J Clin Nutr 67(5):858-66

Mild hyperhomocysteinemia is accepted as a risk factor for premature cardiovascular disease. In a population with a high prevalence of cardiovascular disease, we screened a group of clinically healthy working men aged 30-49 y (n = 509) for plasma homocysteine and 5,10-methylene tetrahydrofolate reductase (MTHFR) genotype status. Those with mildly elevated homocysteine concentrations (> or = 8.34 micromol/L) were selected for intervention. In a randomized, factorial-design, controlled trial we assessed the effects of B-group vitamins and antioxidant vitamin supplementation on homocysteine concentrations. The 132 men were randomly assigned to one of four groups: supplementation with B-group vitamins alone (1 mg folic acid, 7.2 mg pyridoxine, and 0.02 mg cyanocobalamin), antioxidant vitamins alone (150 mg ascorbic acid, 67 mg RRR-alpha-tocopherol, and 9 mg beta-carotene), B-group vitamins with antioxidant vitamins, or placebo. Intervention was double-blind. A total of 101 men completed the 8-wk intervention. When homocysteine concentrations were analyzed by group, significant ($P < 0.001$) decreases (32.0% and 30.0%, respectively) were observed in both groups receiving B-group vitamins either with or without antioxidants. The effect of B-group vitamins alone over 8 wk was a reduction in homocysteine concentrations of 27.9% (95% CI: 22.0%, 33.3%; $P < 0.001$) whereas antioxidants alone produced a nonsignificant increase of 5.1% (95% CI: -2.8%, 13.6%; $P = 0.21$). There was no evidence of any interaction between the two groups of vitamins. The effect of B-group vitamin supplementation seemed to depend on MTHFR genotype. Supplementation with the B-group vitamins with or without antioxidants reduced homocysteine in the men with mildly elevated concentrations, and hence may be effective in reducing cardiovascular risk.

Vitamin E supplementation and cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators.

Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. 2000.
N Engl J Med 342(3):154-60

BACKGROUND: Observational and experimental studies suggest that the amount of vitamin E ingested in food and in supplements is associated with a lower risk of coronary heart disease and atherosclerosis. METHODS: We enrolled a total of 2545 women and 6996 men 55 years of age or older who were at high risk for cardiovascular events because they had cardiovascular disease or diabetes in addition to one other risk factor. These patients were randomly assigned according to a two-by-two factorial design to receive either 400 IU of vitamin E daily from natural sources or matching placebo and either an angiotensin-converting-enzyme inhibitor (ramipril) or matching placebo for a mean of 4.5 years (the results of the comparison of ramipril and placebo are reported in a companion article). The primary outcome was a composite of myocardial infarction, stroke, and death from cardiovascular causes. The secondary outcomes included unstable angina, congestive heart failure, revascularization or amputation, death from any cause, complications of diabetes, and cancer. RESULTS: A total of 772 of the 4761 patients assigned to vitamin E (16.2 percent) and 739 of the 4780 assigned to placebo (15.5 percent) had a primary outcome event (relative risk, 1.05; 95 percent confidence interval, 0.95 to 1.16; P=0.33). There were no significant differences in the numbers of deaths from cardiovascular causes (342 of those assigned to vitamin E vs. 328 of those assigned to placebo; relative risk, 1.05; 95 percent confidence interval, 0.90 to 1.22), myocardial infarction (532 vs. 524; relative risk, 1.02; 95 percent confidence interval, 0.90 to 1.15), or stroke (209 vs. 180; relative risk, 1.17; 95 percent confidence interval, 0.95 to 1.42). There were also no significant differences in the incidence of secondary cardiovascular outcomes or in death from any cause. There were no significant adverse effects of vitamin E. CONCLUSIONS: In patients at high risk for cardiovascular events, treatment with vitamin E for a mean of 4.5 years had no apparent effect on cardiovascular outcomes.

Cancer Prevention

Calcium supplements for the prevention of colorectal adenomas. Calcium Polyp Prevention Study Group.

Baron JA, Beach M, Mandel JS, van Stolk RU, Haile RW, Sandler RS, Rothstein R, Summers RW, Snover DC, Beck GJ, Bond JH, Greenberg ER. 1999.
N Engl J Med 340(2):101-7

BACKGROUND AND METHODS: Laboratory, clinical, and epidemiologic evidence suggests that calcium may help prevent colorectal adenomas. We conducted a randomized, double-blind trial of the effect of supplementation with calcium carbonate on the recurrence of colorectal adenomas. We randomly assigned 930 subjects (mean age, 61 years; 72 percent men) with a recent history of colorectal adenomas to receive either calcium carbonate (3 g [1200 mg of elemental calcium] daily) or placebo, with follow-up colonoscopies one and four years after the qualifying examination. The primary end point was the proportion of subjects in whom at least one adenoma was detected after the first follow-up endoscopy but up to (and including) the second follow-up examination. Risk ratios for the recurrence of adenomas were adjusted for age, sex, lifetime number of adenomas before the study, clinical center, and length of the surveillance period. RESULTS: The subjects in the calcium group had a lower risk of recurrent adenomas. Among the 913 subjects who underwent at least one study colonoscopy, the adjusted risk ratio for any recurrence of adenoma with calcium as compared with placebo was 0.85 (95 percent confidence interval, 0.74 to 0.98; P=0.03). The main analysis was based on the 832 subjects (409 in the calcium group and 423 in the placebo group) who completed both follow-up examinations. At least one adenoma was diagnosed between the first and second follow-up endoscopies in 127 subjects in the calcium group (31 percent) and 159 subjects in the placebo group (38 percent); the adjusted risk ratio was 0.81 (95 percent confidence interval, 0.67 to 0.99; P=0.04). The adjusted ratio of the average number of adenomas in the calcium group to that in the placebo group was 0.76 (95 percent confidence interval, 0.60 to 0.96; P=0.02). The effect of calcium was independent of initial dietary fat and calcium intake. CONCLUSIONS: Calcium supplementation is associated with a significant - though moderate reduction in the risk of recurrent colorectal adenomas.

Regression of oral leukoplakia with alpha-tocopherol: a community clinical oncology program chemoprevention study.

Benner SE, Winn RJ, Lippman SM, Poland J, Hansen KS, Luna MA, Hong WK. 1993.
J Natl Cancer Inst 85(1):44-7

BACKGROUND: Oral leukoplakia is an important model for developing chemoprevention approaches for lesions in the upper aerodigestive tract. These lesions most often result from exposure to carcinogens such as tobacco and alcohol and may precede development of invasive cancer. The potent antioxidant alpha-tocopherol (vitamin E) has prevented the development of cancers of the oral cavities in animal models. PURPOSE: The objectives of this study were to evaluate the toxicity and efficacy of alpha-tocopherol in patients with oral leukoplakia and to assess the feasibility of performing chemoprevention trials through the network of the Community Clinical Oncology Program (CCOP). METHODS: A single-arm phase II study using the nontoxic agent alpha-tocopherol to treat oral premalignant leukoplakia was performed at seven institutions affiliated with the CCOP through The University of Texas M. D. Anderson Cancer Center. Patients with symptomatic leukoplakia or dysplasia were treated orally with alpha-tocopherol (400 IU) twice daily for 24 weeks. Follow-up was performed at 6, 12, and 24 weeks after the start of treatment to assess toxicity and response, and serum alpha-tocopherol levels were determined at baseline and at 6 and 24 weeks. RESULTS: Of the 43 patients who have completed 24 weeks of treatment, 20 (46%) had clinical responses and nine (21%) had histologic responses. Mean serum alpha-tocopherol levels were 16.1 micrograms/mL at baseline and increased to 34.29 micrograms/mL after 24 weeks of treatment. Patient-recorded drug calendars, as well as serum drug levels, indicated excellent patient compliance; an average of 95% of the prescribed pills were taken. Treatment was extremely well tolerated; no grade 3 or 4 toxic effects were reported. CONCLUSIONS: Administration of alpha-tocopherol resulted in both clinical and histologic responses in premalignant leukoplakia lesions. The study also demonstrated that chemoprevention trials can be performed through the CCOP. The major problems were that a high percentage of patients were not assessable for response, some patients withdrew because expenses were not reimbursable, and there was limited participation within the CCOP network. These problems may reflect difficulties inherent in the implementation of multi-institutional chemoprevention trials. IMPLICATIONS: The efficacy of alpha-tocopherol alone and in combination with other chemopreventive agents for carcinogenesis in the upper aerodigestive tract should be explored in future trials.

Reduced risk of colon cancer with high intake of vitamin E: the Iowa Women's Health Study.

Bostick RM, Potter JD, McKenzie DR, Sellers TA, Kushi LH, Steinmetz KA, Folsom AR. 1993.
Cancer Res 53(18):4230-7

Antioxidant micronutrients, including vitamin E, vitamin C, the carotenoids, and selenium, defend the body against free radicals and reactive oxygen molecules, suggesting a potential for these dietary components in cancer prevention. To investigate whether high intakes of antioxidant micronutrients protect against colon cancer in humans, we analyzed data from a prospective cohort study of 35,215 Iowa women aged 55-69 years and without a history of cancer who completed a dietary questionnaire in 1986. Through 1990, 212 incident cases of colon cancer were documented. Adjusted for age, total vitamin E intake was inversely associated with the risk of colon cancer (P for trend < 0.0001); the relative risk for the highest compared to the lowest quintile was 0.32 [95% confidence interval (95% CI) 0.19, 0.54]. Further adjustment for total energy intake and other risk factors in proportional hazards regression had little effect on these estimates. The association was not uniform across age groups: the multivariate relative risk of colon cancer for the highest compared to the lowest quintile of total vitamin E intake was 0.16 (95% CI 0.04, 0.70) for those 55-59 years old, 0.37 (95% CI 0.12, 1.16) for those 60-64 years old, and 0.93 (95% CI 0.27, 3.25) for those 65-69 years old. Multivariate-adjusted relative risks among women with higher total intakes of vitamins A and C and beta-carotene, and among users of selenium supplements, were not significantly different from 1.0. These prospective data provide evidence that a high intake of vitamin E may decrease the risk of colon cancer, especially in persons under 65 years of age.

Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group.

Clark LC, Combs GF Jr, Turnbull BW, Slate EH, Chalker DK, Chow J, Davis LS, Glover RA, Graham GF, Gross EG, Krongrad A, Lesher JL Jr, Park HK, Sanders BB Jr, Smith CL, Taylor JR. 1996.
JAMA 276(24):1957-63

OBJECTIVE: To determine whether a nutritional supplement of selenium will decrease the incidence of cancer. DESIGN: A multicenter, double-blind, randomized, placebo-controlled cancer prevention trial. SETTING: Seven dermatology clinics in the eastern United States. PATIENTS: A total of 1312 patients (mean age, 63 years; range, 18-80 years) with a history of basal cell or squamous cell carcinomas of the skin were randomized from 1983 through 1991. Patients were treated for a mean (SD) of 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years. INTERVENTIONS: Oral administration of 200 microg of selenium per day or placebo. MAIN OUTCOME MEASURES: The primary end points for the trial were the incidences of basal and squamous cell carcinomas of the skin. The secondary end points, established in 1990, were all-cause mortality and total cancer mortality, total cancer incidence, and the incidences of lung, prostate, and colorectal cancers. RESULTS: After a total follow-up of 8271 person-years, selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. There were 377 new cases of basal cell skin cancer among patients in the selenium group and 350 cases among the control group (relative risk [RR], 1.10; 95% confidence interval [CI], 0.95-1.28), and 218 new squamous cell skin cancers in the selenium group and 190 cases among the controls (RR, 1.14; 95% CI, 0.93-1.39). Analysis of secondary end points revealed that, compared with controls, patients treated with selenium had a nonsignificant reduction in all-cause mortality (108 deaths in the selenium group and 129 deaths in the control group [RR; 0.83; 95% CI, 0.63-1.08]) and significant reductions in total cancer mortality (29 deaths in the selenium treatment group and 57 deaths in controls [RR, 0.50; 95% CI, 0.31-0.80]), total cancer incidence (77 cancers in the selenium group and 119 in controls [RR, 0.63; 95% CI, 0.47-0.85]), and incidences of lung, colorectal, and prostate cancers. Primarily because of the apparent reductions in total cancer mortality and total cancer incidence in the selenium group, the blinded phase of the trial was stopped early. No cases of selenium toxicity occurred. CONCLUSIONS: Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites. These effects of selenium require confirmation in an independent trial of appropriate design before new public health recommendations regarding selenium supplementation can be made.

Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial.

Clark LC, Dalkin B, Krongrad A, Combs GF Jr, Turnbull BW, Slate EH, Witherington R, Herlong JH, Janosko E, Carpenter D, Borosso C, Falk S, Rounder J. 1998.
Br J Urol 81(5):730-4

OBJECTIVE: To test if supplemental dietary selenium is associated with changes in the incidence of prostate cancer. PATIENTS AND METHOD: A total of 974 men with a history of either a basal cell or squamous cell carcinoma were randomized to either a daily supplement of 200 microg of selenium or a placebo. Patients were treated for a mean of 4.5 years and followed for a mean of 6.5 years. RESULTS: Selenium treatment was associated with a significant (63%) reduction in the secondary endpoint of prostate cancer incidence during 1983-93. There were 13 prostate cancer cases in the selenium-treated group and 35 cases in the placebo group (relative risk, RR=0.37, P=0.002). Restricting the analysis to the 843 patients with initially normal levels of prostate-specific antigen (< or = 4 ng/mL), only four cases were diagnosed in the selenium-treated group and 16 cases were diagnosed in the placebo group after a 2 year treatment lag, (RR=0.26 P=0.009). There were significant health benefits also for the other secondary endpoints of total cancer mortality, and the incidence of total, lung and colorectal cancer. There was no significant change in incidence for the primary endpoints of basal and squamous cell carcinoma of the skin. In light of these results, the 'blinded' phase of this trial was stopped early. CONCLUSIONS: Although selenium shows no protective effects against the primary endpoint of squamous and basal cell carcinomas of the skin, the selenium-treated group had substantial reductions in the incidence of prostate cancer, and total cancer incidence and mortality that demand further evaluation in well-controlled prevention trials.

Vitamin supplement use and reduced risk of oral and pharyngeal cancer.

Gridley G, McLaughlin JK, Block G, Blot WJ, Gluch M, Fraumeni JF Jr. 1992.
Am J Epidemiol 135(10):1083-92

Use of vitamin and mineral supplements was assessed in a population-based case-control study of oral and pharyngeal cancer, conducted during 1984-1985 in four areas of the United States. There was no association with intake of multivitamin products, but users of supplements of individual vitamins, including vitamins A, B, C, and E, were at lower risk after controlling for the effects of tobacco, alcohol, and other risk factors for these cancers. After further adjustment for use of other supplements, vitamin E was the only supplement that remained associated with a significantly reduced cancer risk. The adjusted odds ratio of oral and pharyngeal cancer for "ever regularly used" vitamin E was 0.5 (95% confidence interval 0.4-0.6). To the authors' knowledge, this is the first epidemiologic study to show a reduced oral cancer risk with vitamin E use. Although it is not clear that the lower risk among consumers of vitamin E supplements is due to the vitamin per se, the findings are consistent with experimental evidence and should prompt further research on the role of vitamin E and other micronutrients as inhibitors of oral and pharyngeal cancer.

Vitamin and mineral supplement use is associated with reduced risk of prostate cancer.

Kristal AR, Stanford JL, Cohen JH, Wicklund K, Patterson RE. 1999.
Cancer Epidemiol Biomarkers Prev 8(10):887-92

This population-based, case-control study in King County, Washington examined supplement use in 697 incident prostate cancer cases (ages 40-64) identified from the Puget Sound Surveillance, Epidemiology and End Results program registry and 666 controls recruited from the same overall population using random-digit dialing sampling. Participants reported their frequency of use of three types of multivitamins and single supplements of vitamins A, C, and E, calcium, iron, and zinc over the 2 years before diagnosis. Logistic regression analyses controlled for age, race, education, family history of prostate cancer, body mass index, number of prostate-specific antigen tests in the previous 5 years, and dietary fat intake. Adjusted odds ratios (95% confidence limits) for the contrast of > or =7/week versus no use were as follows: multivitamins, 0.96 (0.73, 1.26); vitamin A, 0.59 (0.32, 1.06); vitamin C, 0.77 (0.57, 1.04); vitamin E, 0.76 (0.54, 1.08); calcium, 1.04 (0.61, 1.78); iron, 0.50 (0.13, 1.76); and zinc, 0.55 (0.30, 1.00). Odds ratios differed little when cases were stratified by stage of disease at diagnosis or by histopathological grade. There were significant dose-response effects for zinc and ordered dose-response trends for vitamins C and E. Overall, these results suggest that multivitamin use is not associated with prostate cancer risk, but use of individual supplements of zinc, vitamin C, and vitamin E may be protective. Further study is needed to investigate the direct role of these dietary supplements, as well as the role of lifestyle variables associated with supplement use, on prostate cancer risk.

Lack of effect of a low-fat, high-fiber diet on the recurrence of colorectal adenomas. Polyp Prevention Trial Study Group.

Schatzkin A, Lanza E, Corle D, Lance P, Iber F, Caan B, Shike M, Weissfeld J, Burt R, Cooper MR, Kikendall JW, Cahill J. 2000.
Polyp Prevention Trial Study Group. N Engl J Med 342(16):1149-55

BACKGROUND: We tested the hypothesis that dietary intervention can inhibit the development of recurrent colorectal adenomas, which are precursors of most large-bowel cancers. METHODS: We randomly assigned 2079 men and women who were 35 years of age or older and who had had one or more histologically confirmed colorectal adenomas removed within six months before randomization to one of two groups: an intervention group given intensive counseling and assigned to follow a diet that was low in fat (20 percent of total calories) and high in fiber (18 g of dietary fiber per 1000 kcal) and fruits and vegetables (3.5 servings per 1000 kcal), and a control group given a standard brochure on healthy eating and assigned to follow their usual diet. Subjects entered the study after undergoing complete colonoscopy and removal of adenomatous polyps; they remained in the study for approximately four years, undergoing colonoscopy one and four years after randomization. RESULTS: A total of 1905 of the randomized subjects (91.6 percent) completed the study. Of the 958 subjects in the intervention group and the 947 in the control group who completed the study, 39.7 percent and 39.5 percent, respectively, had at least one recurrent adenoma; the unadjusted risk ratio was 1.00 (95 percent confidence interval, 0.90 to 1.12). Among subjects with recurrent adenomas, the mean (+/-SE) number of such lesions was 1.85+/-0.08 in the intervention group and 1.84+/-0.07 in the control group. The rate of recurrence of large adenomas (with a maximal diameter of at least 1 cm) and advanced adenomas (defined as lesions that had a maximal diameter of at least 1 cm or at least 25 percent villous elements or evidence of high-grade dysplasia, including carcinoma) did not differ significantly between the two groups. CONCLUSIONS: Adopting a diet that is low in fat and high in fiber, fruits, and vegetables does not influence the risk of recurrence of colorectal adenomas.

Strong Bones

Vitamin D3 and calcium to prevent hip fractures in the elderly women.

Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. 1992.
N Engl J Med 327(23):1637-42

BACKGROUND. Hypovitaminosis D and a low calcium intake contribute to increased parathyroid function in elderly persons. Calcium and vitamin D supplements reduce this secondary hyperparathyroidism, but whether such supplements reduce he risk of hip fractures among elderly people is not known. METHODS. We studied the effects of supplementation with vitamin D3 (cholecalciferol) and calcium on the frequency of hip fractures and other nonvertebral fractures, identified radiologically, in 3270 healthy ambulatory women (mean [+/- SD] age, 84 +/- 6 years). Each day for 18 months, 1634 women received tricalcium phosphate (containing 1.2 g of elemental calcium) and 20 micrograms (800 IU) of vitamin D3, and 1636 women received a double placebo. We measured serial serum parathyroid hormone and 25-hydroxyvitamin D (25(OH)D) concentrations in 142 women and determined the femoral bone mineral density at base line and after 18 months in 56 women. RESULTS. Among the women who completed the 18-month study, the number of hip fractures was 43 percent lower (P = 0.043) and the total number of nonvertebral fractures was 32 percent lower (P = 0.015) among the women treated with vitamin D3 and calcium than among those who received placebo. The results of analyses according to active treatment and according to intention to treat were similar. In the vitamin D3-calcium group, the mean serum parathyroid hormone concentration had decreased by 44 percent from the base-line value at 18 months (P < 0.001) and the serum 25(OH)D concentration had increased by 162 percent over the base-line value (P < 0.001). The bone density of the proximal femur increased 2.7 percent in the vitamin D3-calcium group and decreased 4.6 percent in the placebo group (P < 0.001). CONCLUSIONS. Supplementation with vitamin D3 and calcium reduces the risk of hip fractures and other nonvertebral fractures among elderly women.

Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D.

Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. 1995.
Am J Clin Nutr 61(5):1140-5

We conducted a study to determine whether increasing vitamin D intake above the recommended dietary allowance (RDA) of 5.0 micrograms (200 IU)/d reduces bone loss in healthy postmenopausal women residing at latitude 42 degrees N. In this double-blind, randomized 2-y trial, we enrolled 247 healthy ambulatory postmenopausal women who consumed an average of 2.5 micrograms (100 IU) vitamin D/d in their usual diets. The women were given either 2.5 micrograms (100 IU) or 17.5 micrograms (700 IU) vitamin D/d. All women received 500 mg supplemental calcium per day as citrate malate. Duplicate hip and spine and single whole-body scans were performed by dual-energy x-ray absorptiometry at 6-mo intervals selected to flank the periods when 25-hydroxycholecalciferol (calcidiol) concentrations are highest (summer/fall) and lowest (winter/spring). Plasma calcidiol and serum osteocalcin were measured in these seasons in year 1. Both treatment groups lost bone mineral density from the femoral neck, but the 17.5-micrograms group lost less than (-1.06 +/- 0.34%; mean +/- SE) the 2.5-micrograms group (-2.54 +/- 0.37%, P = 0.003). Seventy percent of the benefit each year occurred in winter/spring and 30% in summer/fall. Changes in spinal and whole-body bone densities did not differ by treatment group and were minimal after 2 y. Serum osteocalcin and plasma calcidiol (2.5-micrograms group only) fluctuated with season. In conclusion, in healthy, calcium-supplemented, postmenopausal women residing at latitude 42 degrees N, an intake of 5.0 micrograms (200 IU) vitamin D/d is sufficient to limit bone loss from the spine and whole body but it is not adequate to minimize bone loss from the femoral neck.

A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women.

Dawson-Hughes B, Dallal GE, Krall EA, Sadowski L, Sahyoun N, Tannenbaum S. 1990.
N Engl J Med 323(13):878-83

Background. The effectiveness of calcium in retarding bone loss in older postmenopausal women is unclear. Earlier work suggested that the women who were most likely to benefit from calcium supplementation were those with low calcium intakes. METHODS. We undertook a double-blind, placebo-controlled, randomized trial to determine the effect of calcium on bone loss from the spine, femoral neck, and radius in 301 healthy postmenopausal women, half of whom had a calcium intake lower than 400 mg per day and half an intake of 400 to 650 mg per day. The women received placebo or either calcium carbonate or calcium citrate malate (500 mg of calcium per day) for two years. Results. In women who had undergone menopause five or fewer years earlier, bone loss from the spine was rapid and was not affected by supplementation with calcium. Among the women who had been postmenopausal for six years or more and who were given placebo, bone loss was less rapid in the group with the higher dietary calcium intake. In those with the lower calcium intake, calcium citrate malate prevented bone loss during the two years of the study; its effect was significantly different from that of placebo (P less than 0.05) at the femoral neck (mean change in bone density [+/- SE], 0.87 +/- 1.01 percent vs. -2.11 +/- 0.93 percent), radius (1.05 +/- 0.75 percent vs. -2.33 +/- 0.72 percent), and spine (-0.38 +/- 0.82 percent vs. -2.85 +/- 0.77 percent). Calcium carbonate maintained bone density at the femoral neck (mean change in bone density, 0.08 +/- 0.98 percent) and radius (0.24 +/- 0.70 percent) but not the spine (-2.54 +/- 0.85 percent). Among the women who had been postmenopausal for six years or more and who had the higher calcium intake, those in all three treatment groups maintained bone density at the hip and radius and lost bone from the spine. CONCLUSIONS. Healthy older postmenopausal women with a daily calcium intake of less than 400 mg can significantly reduce bone loss by increasing their calcium intake to 800 mg per day. At the dose we tested, supplementation with calcium citrate malate was more effective than supplementation with calcium carbonate.

Calcium supplementation and increases in bone mineral density in children.

Johnston CC Jr, Miller JZ, Slemenda CW, Reister TK, Hui S, Christian JC, Peacock M. 1992.
N Engl J Med 327(2):82-7

BACKGROUND. Increased dietary intake of calcium during childhood, usually as calcium in milk, is associated with increased bone mass in adulthood; the increase in mass is important in modifying the later risk of fracture. Whether the increase is due to the calcium content of milk, however, is not certain. METHODS. We conducted a three-year, double-blind, placebo-controlled trial of the effect of calcium supplementation (1000 mg of calcium citrate malate per day) on bone mineral density in 70 pairs of identical twins (mean [+/- SD] age, 10 +/- 2 years; range, 6 to 14). In each pair, one twin served as a control for the other; 45 pairs completed the study. Bone mineral density was measured by photon absorptiometry at two sites in the radius (at base line, six months, and one, two, and three years) and at three sites in the hip and in the spine (at base line and three years). RESULTS. The mean daily calcium intake of the twins given placebo was 908 mg, and that of the twins given calcium supplements was 1612 mg (894 mg from the diet and 718 mg from the supplement). Among the 22 twin pairs who were prepubertal throughout the study, the twins given supplements had significantly greater increases in bone mineral density at both radial sites (mean difference in the increase in bone mineral density: midshaft radius, 5.1 percent [95 percent confidence interval, 1.5 to 8.7 percent]; distal radius, 3.8 percent [95 percent confidence interval, 1.4 to 6.2 percent]) and in the lumbar spine (increase, 2.8 percent [95 percent confidence interval, 1.1 to 4.5 percent]) after three years; the differences in the increases at two of three femoral sites approached significance (Ward's triangle in the femoral neck, 2.9 percent; greater trochanter, 3.5 percent). Among the 23 pairs who went through puberty or were postpubertal, the twins given supplements received no benefit. CONCLUSIONS. In prepubertal children whose average dietary intake of calcium approximated the recommended dietary allowance, calcium supplementation increased the rate of increase in bone mineral density. If the gain persists, peak bone density should be increased and the risk of fracture reduced.

Calcium supplementation and bone mineral density in adolescent girls.

Lloyd T, Andon MB, Rollings N, Martel JK, Landis JR, Demers LM, Eggli DF, Kieselhorst K, Kulin HE. 1993.
JAMA 270(7):841-4.

OBJECTIVE--To evaluate the effect of calcium supplementation on bone acquisition in adolescent white girls. DESIGN--A randomized, double-blind, placebo-controlled trial of the effect of 18 months of calcium supplementation on bone density and bone mass. SUBJECTS--Ninety-four girls with a mean age of 11.9 + 0.5 years at study entry. SETTING--University hospital in a small town. INTERVENTIONS--Calcium supplementation, 500 mg/d calcium as calcium citrate malate; controls received placebo pills. MAIN OUTCOME MEASURES--Bone mineral density and bone mineral content of the lumbar spine and total body were measured by dual-energy x-ray absorptiometry and calcium excretion from 24-hour urine specimens. RESULTS--Calcium intake from dietary sources averaged 960 mg/d for the entire study group. The supplemented group received, on average, an additional 354 mg/d of calcium. The supplemented group compared with the placebo group had greater increases of lumbar spine bone density (18.7% vs 15.8%; P = .03), lumbar spine bone mineral content (39.4% vs 34.7%; P = .06), total body bone mineral density (9.6% vs 8.3%; P = .05), and 24-hour urinary calcium excretion (90.4 vs 72.9 mg/d; P = .02), respectively. CONCLUSIONS Increasing daily calcium intake from 80% of the recommended daily allowance to 110% via supplementation with calcium citrate malate resulted in significant increases in total body and spinal bone density in adolescent girls. The increase of 24 g of bone gain per year among the supplemented group translates to an additional 1.3% skeletal mass per year during adolescent growth, which may provide protection against future osteoporotic fracture.

A co-twin study of the effect of calcium supplementation on bone density during adolescence.

Nowson CA, Green RM, Hopper JL, Sherwin AJ, Young D, Kaymakci B, Guest CS, Smid M, Larkins RG, Wark JD. 1997.
Osteoporos Int. 7(3):219-25.

The effect of calcium supplementation on bone mineral density (BMD) was evaluated in female twin pairs aged 10-17 years with a mean age of 14 years. Forty-two twin pairs (22 monozygotic, 20 dizygotic; (including one monozygotic pair from a set of triplets) completed at least 6 months of the intervention: 37 pairs to 12 months and 28 pairs to 18 months. BMD was measured by dual-energy X-ray absorptiometry (DXA). In a double-blind manner, one twin in each pair was randomly assigned to receive daily a 1000 mg effervescent calcium tablet (Sandocal 1000), and the other a placebo tablet similar in taste and appearance to the calcium supplement but containing no calcium. Compliance (at least 80% tablets consumed), as measured by tablet count, was 85% in the placebo group and 83% in the calcium group over the 18 months of the study, on average increasing dietary calcium to over 1600 mg/day. There was no within-pair difference in the change in height or weight. When the effect of calcium supplementation on BMD was compared with placebo at approximately 6, 12 and 18 months, it was found that there was a 0.015 +/- 0.007 g/ cm2 greater increase in BMD (1.62 +/- 0.84%) at the spine in those on calcium after 18 months. At the end of the first 6 months there was a significant within-pair difference of 1.53 +/- 0.56% at the spine and 1.27 +/- 0.50% at the hip. However, there were no significant differences in the changes in BMD after the initial effect over the first 6 months. Therefore, we found an increase in BMD at the spine with calcium supplementation in females with a mean age of 14 years. The greatest effect was seen in the first 6 months; thereafter the difference was maintained, but there was no accelerated increase in BMD associated with calcium supplementation. The continuance of the intervention until the attainment of peak bone mass and follow-up after cessation of calcium supplementation will be important in clarifying the optimal timing for increased dietary calcium and the sustained, long-term effects of this intervention.

Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: a randomized controlled trial.

Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. 1995.
Am J Med 98(4):331-5

PURPOSE: To determine the long-term effects of calcium supplements or placebo on bone density in healthy women at least 3 years postmenopause. PATIENTS AND METHODS: Eighty-six women from our previously reported 2-year study agreed to continue on their double-blind treatment allocation (1 g elemental calcium or placebo) for a further 2 years, with 78 women (40 on placebo) reaching the 4-year end point. Median (interquartile range) dietary calcium intakes for the whole group were 700 mg (range 540 to 910) per day at baseline, 670 mg (range 480 to 890) per day at 2 years, and 640 mg (range 460 to 880) per day at 4 years. The bone mineral density (BMD) of the total body, lumbar spine, and proximal femur was measured every 6 months by dual-energy, x-ray absorptiometry. RESULTS: There was a sustained reduction in the rate of loss of total body BMD in the calcium group throughout the 4-year study period (P = 0.002), and bone loss was significantly less in the calcium-treated subjects in years 2 through 4 also (difference between groups 0.25% +/- 0.11% per year, P = 0.02). In the lumbar spine, bone loss was reduced in the calcium group in year 1 (P = 0.004), but not subsequently. There was, however, a significant treatment effect at this site over the whole 4-year period (P = 0.03). In the proximal femur, the benefit from calcium treatment also tended to be greater in the first year and was significant over the 4-year study period in the femoral neck (P = 0.03) and the trochanter (P = 0.01). Nine symptomatic fractures occurred in 7 subjects in the placebo group and 2 fractures in 2 subjects receiving calcium (P = 0.037). CONCLUSIONS: Calcium supplementation produces a sustained reduction in the rate of loss of total body BMD in healthy postmenopausal women.

Effect of calcium supplementation on bone loss in postmenopausal women.

Reid IR, Ames RW, Evans MC, Gamble GD, Sharpe SJ. 1993.
N Engl J Med 328(7):460-4

BACKGROUND. The use of calcium supplements slows bone loss in the forearm and has a beneficial effect on the axial bone density of women in late menopause whose calcium intake is less than 400 mg per day. However, the effect of a calcium supplement of 1000 mg per day on the axial bone density of postmenopausal women with higher calcium intakes is not known. METHODS. We studied 122 normal women at least three years after they had reached menopause who had a mean dietary calcium intake of 750 mg per day. The women were randomly assigned to treatment with either calcium (1000 mg per day) or placebo for two years. The bone mineral density of the total body, lumbar spine, and proximal femur was measured every six months by dual-energy x-ray absorptiometry. Serum and urine indexes of calcium metabolism were measured at base line and after 3, 12, and 24 months. RESULTS. The mean (+/- SE) rate of loss of total-body bone mineral density was reduced by 43 percent in the calcium group (-0.0055 +/-0.0010 g per square centimeter per year) as compared with the placebo group (-0.0097 +/- 0.0010 g per square centimeter per year, P = 0.005). The rate of loss of bone mineral density was reduced by 35 percent in the legs (P = 0.02), and loss was eliminated in the trunk (P = 0.04). Calcium use was of significant benefit in the lumbar spine (P = 0.04), and in Ward's triangle the rate of loss was reduced by 67 percent (P = 0.04). Calcium supplementation had a similar effect whether dietary calcium intake was above or below the mean value for the group. Serum parathyroid hormone concentrations tended to be lower in the calcium group, as were urinary hydroxyproline excretion and serum alkaline phosphatase concentrations. CONCLUSIONS. Calcium supplementation significantly slowed axial and appendicular bone loss in normal post-menopausal women.

Healthy Pregnancies / Healthy Babies

Occurrence of congenital heart defects in relation to maternal multivitamin use.

Botto LD, Mulinare J, Erickson JD. 2000.
Am J Epidemiol 151(9):878-84

The purpose of this study was to assess the relation between maternal multivitamin use and risk for cardiac defects in the offspring, using a population-based approach. The Atlanta Birth Defects Case-Control study is a population-based case-control study of infants born between 1968 and 1980 to mothers residing in metropolitan Atlanta, Georgia. The 958 case infants with nonsyndromic cardiac defects were actively ascertained from multiple sources. The 3,029 infants without birth defects (control infants) were selected from birth certificates by stratified random sampling. Periconceptional multivitamin use, defined as reported regular use of multivitamins from 3 months before pregnancy through the first 3 months of pregnancy, was contrasted with no use during the same time period. Periconceptional multivitamin use was associated with a reduced risk for nonsyndromic cardiac defects in the offspring (odds ratio (OR) = 0.76; 95% confidence interval (Cl): 0.60, 0.97). The risk reduction was strongest for outflow tract defects (OR = 0.46; 95% Cl 0.24, 0.86) and ventricular septal defects (OR = 0.61; 95% Cl: 0.38, 0.99). No risk reduction was evident when multivitamin use was begun after the first month of pregnancy. If these associations are causal, the results suggest that approximately one in four major cardiac defects could be prevented by periconceptional multivitamin use.

Effect of calcium supplementation on pregnancy-induced hypertension and preeclampsia: a meta-analysis of randomized controlled trials.

Bucher HC, Guyatt GH, Cook RJ, Hatala R, Cook DJ, Lang JD, Hunt D. 1996.
JAMA 276(17):1388

OBJECTIVE: To review the effect of calcium supplementation during pregnancy on blood pressure, preeclampsia, and adverse outcomes of pregnancy. DATA SOURCE: We searched MEDLINE and EMBASE for 1966 to May 1994. We contacted authors of eligible trials to ensure accuracy and completeness of data and to identify unpublished trials. STUDY SELECTION: Fourteen randomized trials involving 2459 women were eligible. DATA EXTRACTION: Reviewers working independently in pairs abstracted data and assessed validity according to six quality criteria. DATA SYNTHESIS: Each trial yielded differences in blood pressure change between calcium supplementation and control groups that we weighted by the inverse of the variance. The pooled analysis showed a reduction in systolic blood pressure of -5.40 mm Hg (95% confidence interval [CI], -7.81 to -3.00 mm Hg; P<.001) and in diastolic blood pressure of -3.44 mm Hg (95% CI, -5.20 to -1.68 mm Hg; P<.001). The odds ratio for preeclampsia in women with calcium supplementation compared with placebo was 0.38 (95% CI, 0.22 to 0.65). CONCLUSIONS: Calcium supplementation during pregnancy leads to an important reduction in systolic and diastolic blood pressure and preeclampsia. While pregnant women at risk of preeclampsia should consider taking calcium, many more patient events are needed to confirm calcium's impact on maternal and fetal morbidity.

Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation.

Carlson SE, Werkman SH, Rhodes PG, Tolley EA. 1993.
Am J Clin Nutr 58(1):35-42

Docosahexaenoic acid (DHA; 22:6n-3) is important for normal visual development. We hypothesized that preterm infants fed formulas with marine oil as a source of DHA would have better visual acuity than infants fed formulas without marine oil, as measured by the Teller Acuity Card procedure. Marine oil ($P < 0.001$) and age ($P < 0.0001$) influenced visual acuity, by repeated-measures analysis of variance (ANOVA) corrected for the effect of subject. Marine-oil-supplemented infants had better visual acuity than those fed standard formulas at 2 and 4 mo of age, by Fishers' least-squares difference (LSD). Acuity of both dietary groups improved through 6.5 mo of age, then plateaued. Through 4 mo of age, acuity was inversely related to oxygen supplementation (log10 h) and positively related to DHA status, by general-linear-models (GLM) analysis. After 4 mo of age, birth weight and gestational age were the only variables consistently related to visual acuity by GLM. We conclude that marine-oil-supplemented formula improved visual acuity of preterm infants through 4 mo of age by improving DHA status.

Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: a randomized trial.

Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. 1999.
Lancet 354(9181):810-6

BACKGROUND: Oxidative stress has been implicated in the pathophysiology of pre-eclampsia. This randomised controlled trial investigated the effect of supplementation with vitamins C and E in women at increased risk of the disorder on plasma markers of vascular endothelial activation and placental insufficiency and the occurrence of pre-eclampsia. METHODS: 283 women were identified as being at increased risk of pre-eclampsia by abnormal two-stage uterine-artery doppler analysis or a previous history of the disorder and were randomly assigned vitamin C (1000 mg/day) and vitamin E (400 IU/day) or placebo at 16-22 weeks' gestation. Plasma markers of endothelial activation (plasminogen-activator inhibitor 1 [PAI-1]) and placental dysfunction (PAI-2) were measured every month until delivery. Pre-eclampsia was assessed by the development of proteinuric hypertension. Analyses were done by intention to treat, and in the cohort who completed the study. FINDINGS: Supplementation with vitamins C and E was associated with a 21% decrease in the PAI-1/PAI-2 ratio during gestation (95% CI 4-35, p=0.015). In the intention-to-treat cohort, pre-eclampsia occurred in 24 (17%) of 142 women in the placebo group and 11 (8%) of 141 in the vitamin group (adjusted odds ratio 0.39 [0.17-0.90], p=0.02). In the cohort who completed the study (81 placebo group, 79 vitamin group), the odds ratio for pre-eclampsia was 0.24 (0.08-0.70, p=0.002). INTERPRETATION: Supplementation with vitamins C and E may be beneficial in the prevention of pre-eclampsia in women at increased risk of the disease. Multicentre trials are needed to show whether vitamin supplementation affects the occurrence of pre-eclampsia in low-risk women and to confirm our results in larger groups of high-risk women from different populations.

Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation.

Czeizel AE, Dudas I. 1992.
N Engl J Med 327(26):1832-5

BACKGROUND. The risk of recurrent neural-tube defects is decreased in women who take folic acid or multivitamins containing such during the periconceptional period. The extent to which folic acid supplementation can reduce the first occurrence of defects is not known. METHODS. We conducted a randomized, controlled trial of periconceptional multivitamin supplementation to test the efficacy of this treatment in reducing the incidence of a first occurrence of neural-tube defects. Women planning a pregnancy (in most cases their first) were randomly assigned to receive a single tablet of a vitamin supplement (containing 12 vitamins, including 0.8 mg of folic acid; 4 minerals; and 3 trace elements) or a trace-element supplement (containing copper, manganese, zinc, and a very low dose of vitamin C) daily for at least one month before conception and until the date of the second missed menstrual period or later. RESULTS. Pregnancy was confirmed in 4753 women. The outcome of the pregnancy (whether the fetus or infant had a neural-tube defect or congenital malformation) was known in 2104 women who received the vitamin supplement and in 2052 who received the trace-element supplement. Congenital malformations were significantly more prevalent in the group receiving the trace-element supplement than in the vitamin-supplement group (22.9 per 1000 vs. 13.3 per 1000, P = 0.02). There were six cases of neural-tube defects in the group receiving the trace-element supplement, as compared with none in the vitamin-supplement group (P = 0.029). The prevalence of cleft lip with or without cleft palate was not reduced by periconceptional vitamin supplementation. CONCLUSIONS. Periconceptional vitamin use decreases the incidence of a first occurrence of neural-tube defects.

Folate levels and neural tube defects. Implications for prevention.

Daly LE, Kirke PN, Molloy A, Weir DG, Scott JM. 1995.
JAMA. 274(21):1698-702

Using data from a recent case-control study, a woman's risk of having a child with a neural tube defect (NTD) was found to be associated with early pregnancy red cell folate levels in a continuous dose-response relationship. These findings were used to calculate the reduction in NTD cases that would be expected under two different strategies to raise folate levels. Targeting high-risk individuals has a small effect on the population prevalence but can substantially change an individual's risk. Targeting the population produces a small change in individual risk but has a large effect on the population prevalence. Supplementation of high-risk women would be the most efficient method to implement the high-risk strategy, while food fortification would be preferable for the population approach. The current guidelines for the prevention of NTD are for an increased folic acid intake of 0.4 mg per day. This would result in a 48% reduction in NTDs, which may be near optimal. The two intervention strategies should be considered complementary in prevention of NTDs.

Effects of supplementation with omega 3 long-chain polyunsaturated fatty acids on retinal and cortical development in premature infants.

Hoffman DR, Birch EE, Birch DG, Uauy RD. 1993.
Am J Clin Nutr 57(5 Suppl):807S-812S

Deficiency of omega 3 long-chain polyunsaturated fatty acids (LCPUFAs) in vertebrates produces subtle adverse effects on visual and neural function. Preterm infants 1) are deprived of vital intrauterine fat accretion during late pregnancy, 2) must rely solely on formula for fatty acid supplies if not breastfed, and 3) may have limited postnatal desaturase activity. In a study to evaluate the necessity of dietary omega 3 LCPUFAs, preterm infants were fed human milk, corn-oil-based formula (omega 3 fatty acid deficient), soy-oil-based formula (rich in precursor fatty acids), or marine-oil-supplemented formula (containing docosahexaenoic acid). At 36 and 57 wk postconception, the LCPUFA profiles in red blood cell lipids were nearly equivalent in the human-milk and marine-oil groups whereas the corn-oil group had markedly lower values for omega 3 fatty acids. Rod photoreceptor function was significantly less mature in the corn-oil group compared with the human-milk and marine-oil-enriched groups in early postnatal development (36 wk). The corn-oil group also had impaired visual acuity at both 36 and 57 wk. The potential benefit of omega 3 LCPUFA-enriched full-term formula is discussed. The study supports a role for omega 3 LCPUFAs as required nutrients for the optimal maturation of visual and cortical function in preterm infants.

Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects.

Milunsky A, Jick H, Jick SS, Bruell CL, MacLaughlin DS, Rothman KJ, Willett W. 1989.
JAMA 262(20):2847-52

We examined the relation of multivitamin intake in general, and folic acid in particular, to the risk of neural tube defects in a cohort of 23,491 women undergoing maternal serum alpha-fetoprotein screening or amniocentesis around 16 weeks of gestation. Complete questionnaires and subsequent pregnancy outcome information was obtained in 22,776 pregnancies, 49 of which ended in a neural tube defect. The prevalence of neural tube defect was 3.5 per 1000 among women who never used multivitamins before or after conception or who used multivitamins before conception only. The prevalence of neural tube defects for women who used folic acid-containing multivitamins during the first 6 weeks of pregnancy was substantially lower--0.9 per 1000 (prevalence ratio, 0.27; 95% confidence interval, 0.12 to 0.59 compared with never users). For women who used multivitamins without folic acid during the first 6 weeks of pregnancy and women who used multivitamins containing folic acid beginning after 7 or more weeks of pregnancy, the prevalences were similar to that of the nonusers and the prevalence ratios were close to 1.0.

Prevention of neural tube defects: results of the Medical Research Council Vitamin Study.

MRC Vitamin Study Research Group. 1991.
Lancet 338(8760):131-7

A randomised double-blind prevention trial with a factorial design was conducted at 33 centres in seven countries to determine whether supplementation with folic acid (one of the vitamins in the B group) or a mixture of seven other vitamins (A,D,B1,B2,B6,C and nicotinamide) around the time of conception can prevent neural tube defects (anencephaly, spina bifida, encephalocele). A total of 1817 women at high risk of having a pregnancy with a neural tube defect, because of a previous affected pregnancy, were allocated at random to one of four groups--namely, folic acid, other vitamins, both, or neither. 1195 had a completed pregnancy in which the fetus or infant was known to have or not have a neural tube defect; 27 of these had a known neural tube defect, 6 in the folic acid groups and 21 in the two other groups, a 72% protective effect (relative risk 0.28, 95% confidence interval 0.12-0.71). The other vitamins showed no significant protective effect (relative risk 0.80, 95% Cl 0.32-1.72). There was no demonstrable harm from the folic acid supplementation, though the ability of the study to detect rare or slight adverse effects was limited. Folic acid supplementation starting before pregnancy can now be firmly recommended for all women who have had an affected pregnancy, and public health measures should be taken to ensure that the diet of all women who may bear children contains an adequate amount of folic acid.

Periconceptional use of multivitamins and the occurrence of neural tube defects.

Mulinare J, Cordero JF, Erickson JD, Berry RJ. 1988.
JAMA 260(21):3141-5

We studied the association between multivitamin use during the periconceptional period and the occurrence of neural tube defects using data from the Atlanta Birth Defects Case-Control Study. There were 347 babies with neural tube defects who were live born or stillborn to residents of metropolitan Atlanta from 1968 through 1980. The 2829 control-babies born without birth defects were randomly selected through birth certificates. Periconceptional multivitamin use was defined as reported use for each of the three months before conception through the first three months of pregnancy. Mothers who reported not using multivitamins any time during the six-month period were defined as nonusers. Fourteen percent of mothers reported periconceptional multivitamin use and 40% reported nonuse. Multivitamin users were different from nonusers in a number of demographic, health-related, and life-style characteristics. We found an overall apparent protective effect of periconceptional multivitamin use on the occurrence of neural tube defects, with a crude estimated relative risk of 0.40 (95% confidence interval, 0.25 to 0.63). At this time, it is not possible to determine whether this apparently lower risk is the direct result of multivitamin use or the result of other characteristics of women who use multivitamins.

Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy.

Scholl TO, Hediger ML, Bendich A, Schall JI, Smith WK, Krueger PM. 1997.
Am J Epidemiol 146(2):134-41

The objective of this study was to examine the association of prenatal multivitamin/mineral supplement use during the first and second trimesters of pregnancy by low income, urban women in the Camden Study (1985-1995, n = 1,430) and preterm delivery (< 37 completed weeks) and infant low birth weight (< 2,500 g). Prenatal supplement use was corroborated by assay of circulating micronutrients at entry to care (no differences) and week 28 gestation (increased concentrations of folate and ferritin for supplement users). Compared with women who entered care during the first or second trimester but did not use prenatal supplements, supplement use starting in the first or second trimester was associated with approximately a twofold reduction in risk of preterm delivery. After controlling for potential confounding variables, risk of very preterm delivery (< 33 weeks' gestation) was reduced more than fourfold for first trimester users and approximately twofold when use dated from the second trimester. Infant low birth weight and very low birth weight (< 1,500 g) risks were also reduced. Risk of low birth weight was reduced approximately twofold with supplement use during the first and second trimester. Diminution in risk was greater for very low birth weight infants, amounting to a sevenfold reduction in risk of very low birth weight with first trimester supplementation and a greater than sixfold reduction when supplement use started in the second trimester. Thus, in low income, urban women, use of prenatal multivitamin/mineral supplements may have the potential to diminish infant morbidity and mortality.

Periconceptional folic acid exposure and risk of occurrent neural tube defects.

Werler MM, Shapiro S, Mitchell AA. 1993.
JAMA 269(10):1257-61

OBJECTIVES--A recent controlled trial has established that use of a 4-mg folic acid supplement before and during early pregnancy reduces the risk of recurrent neural tube defects (NTDs) by 72%. The present study was designed to determine whether folic acid also reduces the risk of first (occurrent) NTDs. DESIGN--Case-control study. SETTING--Tertiary and birth hospitals in metropolitan areas of Boston, Mass, Philadelphia, Pa, and Toronto, Ontario. PARTICIPANTS- Mothers of 436 occurrent cases with NTDs and mothers of 2615 controls with other major malformations. MAIN OUTCOME MEASURES--The prevalence of use of multivitamins containing folic acid was compared between mothers of cases and controls. RESULTS--The mothers of 17% of cases and 3% of controls reported knowledge of the folic acid-NTD hypothesis and were excluded from further analysis. For daily use of a multivitamins containing folic acid in the periconceptional period (28 days before through 28 days after the last menstrual period), the relative risk (RR) (and 95% confidence interval) was 0.4 (0.2 to 0.6). The most commonly used dose of folic acid was 0.4 mg, and the RR estimate was 0.3 (95% confidence interval, 0.1 to 0.6). For dietary folate, there was a dose-related decline in risk according to the quintile of intake (P for trend = .02). CONCLUSION--These findings suggest that daily periconceptional intake of 0.4 mg of folic acid (the dose most commonly contained in over-the-counter multivitamin preparations) reduces the risk of occurrent NTDs by approximately 60%. A relatively high dietary intake of folate may also reduce the risk.

Sound Metabolism

Effects of psyllium on glucose and serum lipid responses in men with type 2 diabetes and hypercholesterolemia.

Anderson JW, Allgood LD, Turner J, Oeltgen PR, Daggy BP. 1999.
Am J Clin Nutr 70(4):466-73

BACKGROUND: Water-soluble dietary fibers decrease postprandial glucose concentrations and decrease serum cholesterol concentrations. This study examined the effects of administering psyllium to men with type 2 diabetes. OBJECTIVE: The objective was to evaluate the safety and effectiveness of psyllium husk fiber used adjunctively to a traditional diet for diabetes in the treatment of men with type 2 diabetes and mild-to-moderate hypercholesterolemia. DESIGN: After a 2-wk dietary stabilization phase, 34 men with type 2 diabetes and mild-to-moderate hypercholesterolemia were randomly assigned to receive 5.1 g psyllium or cellulose placebo twice daily for 8 wk. Serum lipid and glycemic indexes were evaluated biweekly on an outpatient basis and at weeks 0 and 8 in a metabolic ward. RESULTS: In the metabolic ward, the psyllium group showed significant improvements in glucose and lipid values compared with the placebo group. Serum total and LDL-cholesterol concentrations were 8.9% ($P < 0.05$) and 13.0% ($P = 0.07$) lower, respectively, in the psyllium than in the placebo group. All-day and postlunch postprandial glucose concentrations were 11.0% ($P < 0.05$) and 19.2% ($P < 0.01$) lower in the psyllium than in the placebo group. Both products were well tolerated, with no serious adverse events related to treatment reported in either group. CONCLUSION: The addition of psyllium to a traditional diet for persons with diabetes is safe, is well tolerated, and improves glycemic and lipid control in men with type 2 diabetes and hypercholesterolemia.

Elevated intakes of supplemental chromium improve glucose and insulin variables in individuals with type 2 diabetes.

Anderson RA, Cheng N, Bryden NA, Polansky MM, Cheng N, Chi J, Feng J. 1997.
Diabetes 46(11):1786-91

Chromium is an essential nutrient involved in normal carbohydrate and lipid metabolism. The chromium requirement is postulated to increase with increased glucose intolerance and diabetes. The objective of this study was to test the hypothesis that the elevated intake of supplemental chromium is involved in the control of type 2 diabetes. Individuals being treated for type 2 diabetes (180 men and women) were divided randomly into three groups and supplemented with: 1) placebo, 2) 1.92 micromol (100 microg) Cr as chromium picolinate two times per day, or 3) 9.6 micromol (500 microg) Cr two times per day. Subjects continued to take their normal medications and were instructed not to change their normal eating and living habits. HbA1c values improved significantly after 2 months in the group receiving 19.2 pmol (1,000 microg) Cr per day and was lower in both chromium groups after 4 months (placebo, 8.5 +/- 0.2%; 3.85 micromol Cr, 7.5 +/- 0.2%; 19.2 micromol Cr, 6.6 +/- 0.1%). Fasting glucose was lower in the 19.2-micromol group after 2 and 4 months (4-month values: placebo, 8.8 +/- 0.3 mmol/l; 19.2 micromol Cr, 7.1 +/- 0.2 mmol/l). Two-hour glucose values were also significantly lower for the subjects consuming 19.2 micromol supplemental Cr after both 2 and 4 months (4-month values: placebo, 12.3 +/- 0.4 mmo/l; 19.2 micromol Cr, 10.5 +/- 0.2 mmol/l). Fasting and 2-h insulin values decreased significantly in both groups receiving supplemental chromium after 2 and 4 months. Plasma total cholesterol also decreased after 4 months in the subjects receiving 19.2 micromol/day Cr. These data demonstrate that supplemental chromium had significant beneficial effects on HbA1c, glucose, insulin, and cholesterol variables in subjects with type 2 diabetes. The beneficial effects of chromium in individuals with diabetes were observed at levels higher than the upper limit of the Estimated Safe and Adequate Daily Dietary Intake.

Chromium in the prevention and control of diabetes.

Anderson RA. 2000
Diabetes Metab 26(1):22-7

Chromium is an essential nutrient involved in the metabolism of glucose, insulin and blood lipids. Suboptimal dietary intake of chromium is associated with increased risk factors associated with diabetes and cardiovascular diseases. Within the past five years, chromium has been shown to improve glucose and related variables in subjects with glucose intolerance and type 1, type 2, gestational and steroid-induced diabetes. Severe neuropathy and glucose intolerance of a patient on total parenteral nutrition, who was receiving currently recommended levels of chromium, were reversed by additional supplemental chromium. Chromium increases insulin binding to cells, insulin receptor number and activates insulin receptor kinase leading to increased insulin sensitivity. Additional studies are urgently needed to elucidate the mechanism of action of chromium and its role in the prevention and control of diabetes.

Low-dose guar improves diabetic control.

Jones DB, Slaughter P, Lousley S, Carter RD, Jelfs R, Mann JI. 1985.
J R Soc Med 78(7):546-8

Twenty diabetic outpatients (12 non-insulin-treated and 8 insulin-treated) were given guar granulate in a dose of 10 g daily for two months in order to study the effect on glycaemic control and lipid levels. Mean glycosylated haemoglobin levels (HbA1c%) fell from 11.1 +/- 2.0% pre-guar to 10.5 +/- 2.2% (P less than 0.001) after one month on guar and to 10.1 +/- 2.3% (P less than 0.0001) after two months. Following discontinuation of guar, HbA1c% rose to 11.1 +/- 2.5% (P less than 0.002). However, there were no significant changes in fasting blood glucose, 1 h postprandial blood glucose following a test meal, 24 h urinary glucose excretion or in lipid levels. Gastrointestinal side effects occurred in 4 patients during treatment with guar. Four patients reduced their dose of insulin and 2 patients reduced their dose of sulphonylurea therapy during this time because of symptoms suggestive of hypoglycaemia. We suggest that the low dose of guar used in this study may help improve glycaemic control in diabetic patients and that this may be achieved with a low incidence of gastrointestinal side effects.

Beneficial effects of palatable guar and guar plus fructose diets in diabetic children.

Paganus A, Maenpaa J, Akerblom HK, Stenman UH, Knip M, Simell O. 1987.
Acta Paediatr Scand 76(1):76-81

This randomized cross-over study evaluates the effects of extended, guar and guar + fructose diets on the metabolic balance of children with insulin-dependent diabetes mellitus (IDDM). We studied 22 children; mean age 12.2 years, mean duration of diabetes 4.4 years. The diet was supplement for three weeks with guar in palatable form (5% of daily carbohydrate intake) and with guar + fructose (1 g of fructose/kg body weight, max 30 g/d) for another three weeks. A control group (8 children, mean age 12.3, duration of diabetes 4.3 years) followed the same experimental protocol without guar supplementation. The metabolic balance was assessed by glucosuria index (per cent of tests with less than 1% glucosuria from all urine tests) and measurements of red cell glycohaemoglobin A1c (HbA1c). Serum total and HDL-cholesterol, C-peptide, pancreatic and enteroglucagon were also measured. HbA1c decreased during guar (p less than 0.001) and guar + fructose diet (p less than 0.001). The glucosuria index improved (p less than 0.02) and the serum total cholesterol concentration decreased (p less than 0.02) during the experimental guar diets. Guar in acceptable form and quantity in the diet appears to improve metabolic control of diabetic children.

Robust Immune Function

Effect of vitamin and trace-element supplementation on immune responses and infection in elderly subjects.

Chandra RK. 1992.
Lancet 340(8828):1124-7

Ageing is associated with impaired immune responses and increased infection-related morbidity. This study assessed the effect of physiological amounts of vitamins and trace elements on immunocompetence and occurrence of infection-related illness. 96 independently living, healthy elderly individuals were randomly assigned to receive nutrient supplementation or placebo. Nutrient status and immunological variables were assessed at baseline and at 12 months, and the frequency of illness due to infection was ascertained. Subjects in the supplement group had higher numbers of certain T-cell subsets and natural killer cells, enhanced proliferation response to mitogen, increased interleukin-2 production, and higher antibody response and natural killer cell activity. These subjects were less likely than those in the placebo group to have illness due to infections (mean [SD] 23 [5] vs 48 [7] days per year, p = 0.002). Supplementation with a modest physiological amount of micronutrients improves immunity and decreases the risk of infection in old age.

Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: a randomized controlled trial. MIN. VIT. AOX. geriatric network.

Girodon F, Galan P, Monget AL, Boutron-Ruault MC, Brunet-Lecomte P, Preziosi P, Arnaud J, Manuguerra JC, Herchberg S. 1999.
Arch Intern Med 159(7):748-54

BACKGROUND: Antioxidant supplementation is thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables. OBJECTIVE: To determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people. METHODS: This randomized, double-blind, placebo-controlled intervention study included 725 institutionalized elderly patients (>65 years) from 25 geriatric centers in France. Patients received an oral daily supplement of nutritional doses of trace elements (zinc and selenium sulfide) or vitamins (beta carotene, ascorbic acid, and vitamin E) or a placebo within a 2 x 2 factorial design for 2 years. MAIN OUTCOME MEASURES: Delayed-type hypersensitivity skin response, humoral response to influenza vaccine, and infectious morbidity and mortality. RESULTS: Correction of specific nutrient deficiencies was observed after 6 months of supplementation and was maintained for the first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or associated with vitamins, whereas the vitamin group had significantly lower antibody titers (P<.05). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements (P = .06). Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the 2 years did not show any differences between the 4 groups. CONCLUSIONS: Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.

Effect of micronutrient supplementation on infection in institutionalized elderly subjects: a controlled trial.

Girodon F, Lombard M, Galan P, Brunet-Lecomte P, Monget AL, Arnaud J, Preziosi P, Hercberg S. 1997.
Ann Nutr Metab 41(2):98-107

To determine the impact of a trace element and vitamin supplementation on infectious morbidity, a double-blind controlled trial was performed on 81 elderly subjects in a geriatric center during a 2-year period. Subjects were randomly assigned to one of four treatment groups, and received daily: placebo; trace elements/zinc 20 mg; selenium 100 micrograms); vitamins (vitamin C 120 mg; beta-carotene 6 mg; alpha-tocopherol 15 mg); or a combination of trace elements and vitamins at equal doses. (1) Before supplementation, low serum values in vitamin C, folate, zinc and selenium were observed in more than two thirds of the patients. (2) After 6 months of supplementation, a significant increase in vitamin and trace element serum levels was obtained in the corresponding treatment groups: a plateau was then observed for the whole study. (3) Subjects who received trace elements (zinc and selenium) alone or associated with vitamins had significantly less infectious events during the 2 years of supplementation. These results indicate that supplementation with low doses of vitamins and trace elements is able to rapidly correct corresponding deficiencies in the institutionalized elderly. Moreover, zinc and selenium reduced infectious events.

Vitamin E supplementation enhances cell-mediated immunity in healthy elderly subjects.

Meydani SN, Barklund MP, Liu S, Meydani M, Miller RA, Cannon JG, Morrow FD, Rocklin R, Blumberg JB. 1990.
Am J Clin Nutr 52(3):557-63

The effect of vitamin E supplementation on the immune response of healthy older adults was studied in a double-blind, placebo-controlled trial. Subjects (n = 32) resided in a metabolic research unit and received placebo or vitamin E (800 mg dl-alpha-tocopheryl acetate) for 30 d. Alpha-tocopherol content of plasma and peripheral blood mononuclear cells (PBMCs), delayed-type hypersensitivity skin test (DTH), mitogen-stimulated lymphocyte proliferation, as well as interleukin (IL)-1, IL-2, prostaglandin (PG) E2, and serum lipid peroxides were evaluated before and after treatment. In the vitamin E-supplemented group 1) alpha-tocopherol content was significantly higher (p less than 0.0001) in plasma and PBMCs, 2) cumulative diameter and number of positive antigen responses in DTH response were elevated (p less than 0.05), 3) IL-2 production and mitogenic response to optimal doses of concanavalin A were increased (p less than 0.05), and 4) PGE2 synthesis by PBMCs (p less than 0.005) and plasma lipid peroxides (p less than 0.001) were reduced. Short-term vitamin E supplementation improves immune responsiveness in healthy elderly individuals; this effect appears to be mediated by a decrease in PGE2 and/or other lipid-peroxidation products.

Short- and long-term beta-carotene supplementation do not influence T cell-mediated immunity in healthy elderly persons.

Santos MS, Leka LS, Ribaya-Mercado JD, Russell RM, Meydani M, Hennekens CH, Gaziano JM, Meydani SN. 1997.
Am J Clin Nutr 66(4):917-24

Supplementation of healthy elderly persons with beta-carotene has been considered a way to enhance immune responses. In study 1 the short-term effect of beta-carotene (90 mg/d for 3 wk) on immunity was assessed in a randomized, double-blind, placebo-controlled longitudinal comparison of healthy elderly women. In study 2 the long-term effect of beta-carotene (50 mg every other day for 10-12 y) on immunity was assessed in a randomized, double-blind, placebo-controlled longitudinal comparison of men enrolled in the Physicians' Health Study. Subjects from both studies taking active supplements had significantly greater plasma beta-carotene concentrations than did subjects taking placebo. The pre- to postintervention change in delayed-type hypersensitivity skin test responses between beta-carotene and placebo groups in the short-term study was not significantly different, nor was the response between treatment groups in the long-term study. There were no significant effects due to beta-carotene supplementation on in vitro lymphocyte proliferation, production of interleukin 2, or production of prostaglandin E2 as a result of short- or long-term beta-carotene supplementation. In addition, there were no differences in the profiles of lymphocyte subsets [total T cells (CD3+), T helper cells (CD4+), T cytotoxic-suppressor cells (CD8+), and B cells (CD19+)] due to short- or long-term beta-carotene supplementation, nor were there differences in percentages of CD16+ natural killer cells or activated lymphocytes (cells expressing interleukin 2 transferrin receptor) due to long-term beta-carotene supplementation. Consistent results from these two trials show that beta-carotene supplementation did not have an enhancing or suppressive effect on T cell-mediated immunity of healthy elderly.

Acute Vision

Prospective cohort study of antioxidant vitamin supplement use and the risk of age-related maculopathy.

Christen WG, Ajani UA, Glynn RJ, Manson JE, Schaumberg DA, Chew EC, Buring JE, Hennekens CH. 1999.
Am J Epidemiol 149(5):476-84

In a prospective cohort study, the authors examined whether self-selection for antioxidant vitamin supplement use affects the incidence of age-related maculopathy. The study population consisted of 21,120 US male physician participants in the Physicians' Health Study I who did not have a diagnosis of age-related maculopathy at baseline (1982). During an average of 12.5 person-years of follow-up, a total of 279 incident cases of age-related maculopathy with vision loss to 20/30 or worse were confirmed by medical record review. In multivariate analysis, as compared with nonusers of supplements, persons who used vitamin E supplements had a possible but nonsignificant 13% reduced risk of age-related maculopathy (relative risk = 0.87, 95 percent confidence interval (CI) 0.53-1.43), while users of multivitamins had a possible but nonsignificant 10% reduced risk (relative risk = 0.90, 95% CI 0.68-1.19). Users of vitamin C supplements had a relative risk of 1.03 (95% CI 0.71-1.50). These observational data suggest that among persons who self-select for supplemental use of antioxidant vitamin C or E or multivitamins, large reductions in the risk of age-related maculopathy are unlikely. Randomized trial data are accumulating to enable reliable detection of the existence of more plausible small-to-moderate benefits of these agents alone and in combination on age-related maculopathy.

Long-term vitamin C supplement use and prevalence of early age-related lens opacities.

Jacques PF, Taylor A, Hankinson SE, Willett WC, Mahnken B, Lee Y, Vaid K, Lahav M. 1997.
Am J Clin Nutr 66(4):911-6

We designed the present study to examine the cross-sectional relation between age-related lens opacities and vitamin C supplement use over a 10-12-y period before assessment of lens status in women without diagnosed cataract or diabetes. This design avoids biased measurement of nutrient intake that results when knowledge of lens opacities influences nutrition-related behavior or its reporting. The participants were 247 Boston-area women aged 56-71 y selected from the Nurses' Health Study cohort with oversampling of women with high or low vitamin C intakes. Lens opacities were graded with the Lens Opacification Classification System II. Use of vitamin C supplements for > or = 10 y (n = 26) was associated with a 77% lower prevalence of early lens opacities (odds ratio: 0.23; 95% CI: 0.09, 0.60) at any lens site and a 83% lower prevalence of moderate lens opacities (odds ratio: 0.17; 95% CI: 0.03, 0.85) at any lens site compared with women who did not use vitamin C supplements (n = 141) after adjustment for age and other potentially confounding variables. Women who consumed vitamin C supplements for < 10 y showed no evidence of a reduced prevalence of early opacities. These data, together with data from earlier experimental and epidemiologic studies, suggest that long-term consumption of vitamin C supplements may substantially reduce the development of age-related lens opacities.

A one year study of the macular pigment: the effect of 140 days of a lutein supplement.

Landrum JT, Bone RA, Joa H, Kilburn MD, Moore LL, Sprague KE. 1997.
Exp Eye Res 65(1):57-62

A low density of macular pigment may represent a risk factor for age-related macular degeneration (AMD) by permitting greater blue light damage. This study was carried out to determine the effects on macular pigment optical density of dietary supplementation with lutein, one of the pigment constituents. Two subjects consumed lutein esters, equivalent to 30 mg of free lutein per day, for a period of 140 days. Macular pigment optical density was determined by heterochromatic flicker photometry before, during, and after the supplementation period. Serum lutein concentration was also obtained through the analysis of blood samples by high-performance liquid chromatography. Twenty to 40 days after the subjects commenced taking the lutein supplement, their macular pigment optical density began to increase uniformly at an average rate of 1.13+/-0.12 milliabsorbance units/day. During this same period, the serum concentration of lutein increased roughly tenfold, approaching a steady state plateau. The optical density curve eventually levelled off 40 to 50 days after the subjects discontinued the supplement. During the same 40 to 50 days, the serum concentration returned to baseline. Thereafter, little or no decrease in optical density was observed. The mean increases in the macular pigment optical density were 39% and 21% in the eyes of the two subjects respectively. In conclusion, the modest period of supplementation has been estimated to have produced in the subjects a 30 to 40% reduction in blue light reaching the photoreceptors, Bruch's membrane, and the retinal pigment epithelium, the vulnerable tissues affected by AMD.

Antioxidant vitamins and nuclear opacities: the longitudinal study of cataract.

Leske MC, Chylack LT Jr, He Q, Wu SY, Schoenfeld E, Friend J, Wolfe J. 1998.
Ophthalmology 105(5):831-6

OBJECTIVE: The association of antioxidant nutrients and risk of nuclear opacification was evaluated in the Longitudinal Study of Cataract. DESIGN: Nutritional data were collected at baseline on the 764 participants, which included assessment of dietary intake, use of vitamin supplements, and plasma levels of vitamin E. Ophthalmologic and other data were collected at baseline and at yearly follow-up visits, including lens photographs, which were graded using the Lens Opacities Classification System III protocol. MAIN OUTCOME MEASURES: Analyses examined whether the nutritional factors at baseline were related to increases in nuclear opacification at follow-up. The MULCOX2 approach, an extension of the Cox regression model, was used. Results are presented as relative risks (RRs) and 95% confidence intervals. INTERVENTION: Intervention was not applicable. RESULTS: The risk of nuclear opacification at follow-up was decreased in regular users of multivitamin supplements (RR = 0.69; 0.48-0.99), vitamin E supplements (RR = 0.43; 0.19-0.99), and in persons with higher plasma levels of vitamin E (RR = 0.58; 0.36-0.94). CONCLUSIONS: In regular users of multivitamin supplements, the risk of nuclear opacification was reduced by one third; in regular users of vitamin E supplements and persons with higher plasma levels of vitamin E, the risk was reduced by approximately half. These results are similar to those obtained in our earlier case-control study. Because these data are based on observational studies only, the results are suggestive but inconclusive. The possible effect of nutritional supplements on the lens requires confirmation by ongoing clinical trials.

Vitamin supplement use and incident cataracts in a population-based study.

Mares-Perlman JA, Lyle BJ, Klein R, Fisher AI, Brady WE, VandenLangenberg GM, Trabulsi JN, Palta M. 2000.
Arch Ophthalmol 118(11):1556-63

OBJECTIVE: To determine the relationship between vitamin supplement use and the 5-year incidence of nuclear, cortical, and posterior subcapsular cataract in the Beaver Dam Eye Study cohort. DESIGN: The 5-year incidence of cataract, determined from slitlamp (nuclear cataract) and retroillumination (cortical and posterior subcapsular cataract) photographs, was assessed in a population-based cohort of persons participating in baseline (1988-1990) and follow-up (1993-1995) examinations. Detailed data regarding the type, dosage, and duration of supplement use were obtained by in-person interviews at follow-up. PARTICIPANTS: Residents of Beaver Dam, Wis, aged 43 to 86 years, were identified by private census. Of the 3684 participants in both baseline and follow-up examinations, 3089 were eligible for incident cataract analysis in the present study. RESULTS: Compared with nonusers, the 5-year risk for any cataract was 60% lower among persons who, at follow-up, reported the use of multivitamins or any supplement containing vitamin C or E for more than 10 years. Taking multivitamins for this duration lowered the risk for nuclear and cortical cataracts but not for posterior subcapsular cataracts (odds ratios [95% confidence intervals] = 0.6 [0.4-0.9], 0.4 [0.2-0.8], and 0.9 [0.5-1.9], respectively). Use of supplements for shorter periods was not associated with reduced risk for cataract. Measured differences in lifestyle between supplement users and nonusers did not influence these associations, nor did variations in diet as measured in a random subsample. CONCLUSIONS: These data add to a body of evidence suggesting lower risk for cataract among users of vitamin supplements and stronger associations with long-term use. However, the specific nutrients that are responsible cannot be ascertained at this time, and unmeasured lifestyle differences between supplement users and nonusers may explain these results. Arch Ophthalmol. 2000;118:1556-1563

The use of vitamin supplements and the risk of cataract among US male physicians.

Seddon JM, Christen WG, Manson JE, LaMotte FS, Glynn RJ, Buring JE, Hennekens CH. 1994.
Am J Public Health 84(5):788-92

OBJECTIVES. The purpose of this study was to examine prospectively the association between reported use of vitamin supplements and risk of cataract and cataract extraction. METHODS. The study population consisted of 17,744 participants in the Physicians' Health Study, a randomized trial of aspirin therapy and beta-carotene among US male physicians 40 to 84 years of age in 1982 who did not report cataract at baseline and provided complete information about vitamin supplementation and other risk factors for cataract. Self-reports of cataract and cataract extraction were confirmed by medical record review. RESULTS. During 60 months of follow-up, there were 370 incident cataracts and 109 cataract extractions. In comparison with physicians who did not use any supplements, those who took only multivitamins had a relative risk of cataract of 0.73 after adjustment for other risk factors. For cataract extraction, the corresponding relative risk was 0.79. Use of vitamin C and/or E supplements alone was not associated with a reduced risk of cataract, but the size of this subgroup was small. CONCLUSIONS. These data suggest that men who took multivitamin supplements tended to experience a decreased risk of cataract and support the need for rigorous testing of this hypothesis in large-scale randomized trials in men and women.

Other

The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms.

Bendich A. 2000.
J Am Coll Nutr 19(1):3-12

Many types of dietary supplements have been advocated for the reduction of certain symptoms of premenstrual syndrome (PMS). However, only one supplement-calcium-has been demonstrated to be of significant benefit in a large, rigorous, double-blind, placebo-controlled trial. Limited evidence suggests that magnesium, vitamin E and carbohydrate supplements might also be useful, but additional research is needed to confirm these findings. Trials of vitamin B6 supplementation have had conflicting results, and high doses of this vitamin taken for prolonged periods of time can cause neurological symptoms. Trials of evening primrose oil have also had conflicting results; the two most rigorous studies showed no evidence of benefit. A variety of herbal products are suggested to reduce symptoms of PMS. The efficacy of these products is uncertain because of a lack of consistent data from scientific studies. Health professionals should be aware of the possible use of these supplements and ask those with PMS about their use of such products and counsel them based upon the totality of evidence.

Effect of an enteric-coated fish-oil preparation on relapses in Crohn's disease.

Belluzzi A, Brignola C, Campieri M, Pera A, Boschi S, Miglioli M. 1996.
N Engl J Med 334(24):1557-60

BACKGROUND: Patients with Crohn's disease may have periods of remission, interrupted by relapses. Because fish oil has antiinflammatory actions, it could reduce the frequency of relapses, but it is often poorly tolerated because of its unpleasant taste and gastrointestinal side effects. METHODS: We performed a one-year, double-blind, placebo-controlled study to investigate the effects of a new fish-oil preparation in the maintenance of remission in 78 patients with Crohn's disease who had a high risk of relapse. The patients received either nine fish-oil capsules containing a total of 2.7 g of n-3 fatty acids or nine placebo capsules daily. A special coating protected the capsules against gastric acidity for at least 30 minutes. RESULTS: Among the 39 patients in the fish-oil group, 11 (28 percent) had relapses, 4 dropped out because of diarrhea, and 1 withdrew for other reasons. In contrast, among the 39 patients in the placebo group, 27 (69 percent) had relapses, 1 dropped out because of diarrhea, and 1 withdrew for other reasons (difference in relapse rate, 41 percentage points; 95 percent confidence interval, 21 to 61; $P < 0.001$). After one year, 23 patients (59 percent) in the fish-oil group remained in remission, as compared with 10 (26 percent) in the placebo group ($P = 0.003$). Logistic-regression analysis indicated that only fish oil and not sex, age, previous surgery, duration of disease, or smoking status affected the likelihood of relapse (odds ratio for the placebo group as compared with the fish-oil group, 4.2; 95 percent confidence interval, 1.6 to 10.7). CONCLUSIONS: In patients with Crohn's disease in remission, a novel enteric-coated fish-oil preparation is effective in reducing the rate of relapse.

Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women.

Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. 1997.
Ann Intern Med 126(7):497-504

BACKGROUND: Calcium intake is believed to play an important role in the formation of kidney stones, but data on the risk factors for stone formation in women are limited. OBJECTIVE: To examine the association between intake of dietary and supplemental calcium and the risk for kidney stones in women. DESIGN: Prospective cohort study with 12-year follow-up. SETTING: Several U.S. states. PARTICIPANTS: 91,731 women participating in the Nurses' Health Study I who were 34 to 59 years of age in 1980 and had no history of kidney stones. MEASUREMENTS: Self-administered food-frequency questionnaires were used to assess diet in 1980, 1984, 1986, and 1990. The main outcome measure was incident symptomatic kidney stones. RESULTS: During 903,849 person-years of follow-up, 864 cases of kidney stones were documented. After adjustment for potential risk factors, intake of dietary calcium was inversely associated with risk for kidney stones and intake of supplemental calcium was positively associated with risk. The relative risk for stone formation in women in the highest quintile of dietary calcium intake compared with women in the lowest quintile was 0.65 (95% CI, 0.50 to 0.83). The relative risk in women who took supplemental calcium compared with women who did not was 1.20 (CI, 1.02 to 1.41). In 67% of women who took supplemental calcium, the calcium either was not consumed with a meal or was consumed with meals whose oxalate content was probably low. Other dietary factors showed the following relative risks among women in the highest quintile of intake compared with those in the lowest quintile: sucrose, 1.52 (CI, 1.18 to 1.96); sodium, 1.30 (CI, 1.05 to 1.62); fluid, 0.61 (CI, 0.48 to 0.78); and potassium, 0.65 (CI, 0.51 to 0.84). CONCLUSIONS: High intake of dietary calcium appears to decrease risk for symptomatic kidney stones, whereas intake of supplemental calcium may increase risk. Because dietary calcium reduces the absorption of oxalate, the apparently different effects caused by the type of calcium may be associated with the timing of calcium ingestion relative to the amount of oxalate consumed. However, other factors present in dairy products (the major source of dietary calcium) could be responsible for the decreased risk seen with dietary calcium.

Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid arthritis. Results of a prospective placebo controlled double blind trial.

Edmonds SE, Winyard PG, Guo R, Kidd B, Merry P, Langrish-Smith A, Hansen C, Ramm S, Blake DR. 1997.
Ann Rheum Dis. 56(11):649-55

OBJECTIVE: Vitamin E, the most potent naturally occurring lipid soluble antioxidant has been suggested to possess both anti-inflammatory and analgesic activity in humans. This double blind and randomised study used a broad spectrum of clinical and laboratory parameters to investigate whether there was any additional anti-inflammatory or analgesic effects, or both, of orally administered alpha-tocopherol in rheumatoid arthritis patients who were already receiving anti-rheumatic drugs. METHODS: Forty two patients were enrolled and treated with alpha-tocopherol (n = 20) at a dose of 600 mg twice a day (2 x 2 capsules) or with placebo (n = 22) for 12 weeks. The following parameters were measured: (1) Three clinical indices of inflammation--the Ritchie articular index, the duration of morning stiffness, and the number of swollen joints; (2) three measures of pain--pain in the morning, pain in the evening, and pain after chosen activity; (3) haematological and biochemical measures of inflammatory activity; (4) assays for the oxidative modification of proteins and lipids. RESULTS: All laboratory measures of inflammatory activity and oxidative modification were unchanged. Furthermore, the clinical indices of inflammation were not influenced by the treatment. However, the pain parameters were significantly decreased after vitamin E treatment when compared with placebo. CONCLUSION: The results provide preliminary evidence that vitamin E may exert a small but significant analgesic activity independent of a peripheral anti-inflammatory effect, but which complements standard anti-inflammatory treatment.

Magnesium for the treatment of nocturnal leg cramps: a crossover randomized trial.

Frusso R, Zarate M, Augustovski F, Rubinstein A. 1999.
J Fam Pract 48(11):868-71

BACKGROUND: Nocturnal leg cramps are a common health problem in the ambulatory setting. Our objective was to evaluate the efficacy of magnesium in the treatment of nocturnal leg cramps. METHODS: Our study was a crossover randomized double-blind placebo-controlled trial. We included patients from a large university-based ambulatory clinic in Buenos Aires, Argentina, with at least 6 cramps during the previous month. A total of 93 subjects took part in a 4-week washout period with placebo. Those who were still eligible (n = 45) were randomized to receive either (1) an oral dose of 900 mg magnesium citrate twice daily for 1 month, followed by a matching placebo for 1 month, or (2) the placebo first, followed by magnesium. Both groups had a 4-week washout period with placebo between each treatment month. Forty-two patients completed the 4-month study. The main outcome was the number of nocturnal leg cramps, and the secondary outcomes were duration, severity, and sleep disorders caused by those cramps. RESULTS: There were no significant differences between magnesium and placebo in any of the evaluated outcomes. The mean number of cramps was 11.1 (standard deviation [SD] +/- 7.3) for placebo versus 11.8 (SD +/- 7.6) for magnesium (P = .59). We observed a significant period-effect bias: All patients improved over time regardless of the treatment sequence they received. CONCLUSIONS: Magnesium was not effective for the treatment of nocturnal leg cramps. The period-effect bias probably occurred because of a combination of the natural history of this condition, a regression to the mean, and a true placebo effect.

n-3 fatty acid supplements in rheumatoid arthritis.

Kremer JM. 2000.
Am J Clin Nutr 71(suppl):349S-51S

Ingestion of dietary supplements of n-3 fatty acids has been consistently shown to reduce both the number of tender joints on physical examination and the amount of morning stiffness in patients with rheumatoid arthritis. In these cases, supplements were consumed daily in addition to background medications and the clinical benefits of the n-3 fatty acids were not apparent until they were consumed for > or =12 wk. It appears that a minimum daily dose of 3 g eicosapentaenoic and docosahexaenoic acids is necessary to derive the expected benefits. These doses of n-3 fatty acids are associated with significant reductions in the release of leukotriene B(4) from stimulated neutrophils and of interleukin 1 from monocytes. Both of these mediators of inflammation are thought to contribute to the inflammatory events that occur in the rheumatoid arthritis disease process. Several investigators have reported that rheumatoid arthritis patients consuming n-3 dietary supplements were able to lower or discontinue their background doses of nonsteroidal antiinflammatory drugs or disease-modifying antirheumatic drugs. Because the methods used to determine whether patients taking n-3 supplements can discontinue taking these agents are variable, confirmatory and definitive studies are needed to settle this issue. n-3 Fatty acids have virtually no reported serious toxicity in the dose range used in rheumatoid arthritis and are generally very well tolerated.

A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. The Alzheimer's Disease Cooperative Study.

Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. 1997.
N Engl J Med 336(17):1216-22

BACKGROUND: There is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease. METHODS: We conducted a double-blind, placebo-controlled, randomized, multicenter trial in patients with Alzheimer's disease of moderate severity. A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3). RESULTS: Despite random assignment, the baseline score on the Mini-Mental State Examination was higher in the placebo group than in the other three groups, and this variable was highly predictive of the primary outcome ($P<0.001$). In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. In analyses that included the base-line score on the Mini-Mental State Examination as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline (median time, 655 days; $P=0.012$), alpha-tocopherol (670 days, $P=0.001$) or combination therapy (585 days, $P=0.049$), as compared with the placebo group (440 days). CONCLUSIONS: In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease.

Calcium carbonate and the premenstrual syndrome: effects on premenstrual and menstrual symptoms. Premenstrual Syndrome Study Group.

Thys-Jacobs S, Starkey P, Bernstein D, Tian J. 1998.
Am J Obstet Gynecol 179(2):444-52

OBJECTIVE: Previous reports have suggested that disturbances in calcium regulation may underlie the pathophysiologic characteristics of premenstrual syndrome and that calcium supplementation may be an effective therapeutic approach. To evaluate the effect of calcium carbonate on the luteal and menstrual phases of the menstrual cycle in premenstrual syndrome, a prospective, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical trial was conducted. STUDY DESIGN: Healthy, premenopausal women between the ages of 18 and 45 years were recruited nationally across the United States at 12 outpatient centers and screened for moderate-to-severe, cyclically recurring premenstrual symptoms. Symptoms were prospectively documented over 2 menstrual cycles with a daily rating scale that had 17 core symptoms and 4 symptom factors (negative affect, water retention, food cravings, and pain). Participants were randomly assigned to receive 1200 mg of elemental calcium per day in the form of calcium carbonate or placebo for 3 menstrual cycles. Routine chemistry, complete blood cell count, and urinalysis were obtained on all participants. Daily documentation of symptoms, adverse effects, and compliance with medications were monitored. The primary outcome measure was the 17-parameter symptom complex score. RESULTS: Seven hundred twenty women were screened for this trial; 497 women were enrolled; 466 were valid for the efficacy analysis. There was no difference in age, weight, height, use of oral contraceptives, or menstrual cycle length between treatment groups. There were no differences between groups in the mean screening symptom complex score of the luteal ($P = .659$), menstrual ($P = .818$), or intermenstrual phase ($P = .726$) of the menstrual cycle. During the luteal phase of the treatment cycle, a significantly lower mean symptom complex score was observed in the calcium-treated group for both the second ($P = .007$) and third ($P < .001$) treatment cycles. By the third treatment cycle calcium effectively resulted in an overall 48% reduction in total symptom scores from baseline compared with a 30% reduction in placebo. All 4 symptom factors were significantly reduced by the third treatment cycle. CONCLUSIONS: Calcium supplementation is a simple and effective treatment in premenstrual syndrome, resulting in a major reduction in overall luteal phase symptoms.