

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 \pm 1.4; 2 hours, 25.4 \pm 2.5; and 4 hours, 31.2 \pm 3.1 micromol/l, P <0.001), and flow-mediated dilatation fell (0 hours, 4.3 \pm 0.7; 2 hours, 1.1 \pm 0.9; and 4 hours, -0.7 \pm 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 \pm 1.6; 2 hours, 28.3 \pm 2.9; and 4 hours, 33.8 \pm 3.7 micromol/l, P =0.27), but did ameliorate the reduction in flow-mediated dilatation (0 hours, 4.0 \pm 1.0; 2 hours, 3.5 \pm 1.2 and 4 hours, 2.8 \pm 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, Boisseau M, 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, Keane 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 \pm 3.5% to 10.1 \pm 5.2% after single-dose treatment, and the effect was sustained after long-term treatment (9.0 \pm 3.7%), whereas flow-mediated dilation was 8.6 \pm 4.7% at baseline and remained unchanged after single-dose (7.8 \pm 4.4%) and long-term (7.9 \pm 4.5%) treatment with placebo (P=0.005 by repeated-measures ANOVA). Plasma ascorbic acid concentrations increased from 41.4 \pm 12.9 to 115.9 \pm 34.2 micromol/L after single-dose treatment and to 95.0 \pm 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 \pm 0.12 to 0.12 \pm 0.07 mm, p < 0.05) and a significant reduction in triglycerides (2.07 \pm 1.13 to 1.73 \pm 0.95 mmol/liter, p < 0.05), whereas treatment with placebo resulted in no change in FMD (0.03 \pm 0.10 to 0.04 \pm 0.10 mm) or triglycerides (2.29 \pm 2.09 to 2.05 \pm 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 \pm 1.7% versus 8.2 \pm 1.0%; $P < .01$) and after 4 weeks of oral therapy (11.9 \pm 0.9% versus 8.2 \pm 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 \pm 0.7%; acute: 9.1 \pm 1.3%; chronic: 7.3 \pm 1.2%; normal subjects: 8.9 \pm 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, Keane 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=0.001). 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=0.003 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 peroxy-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% CI 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 $\mu\text{mol/L}$). **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 $\mu\text{mol/L}$ vs from 14.7 to 12.0 $\mu\text{mol/L}$), and in postmethionine homocysteine concentration (from 64.9 to 34.9 $\mu\text{mol/L}$ vs from 64.8 to 50.3 $\mu\text{mol/L}$). 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 (≥ 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.