

STROKE (HEMORRHAGIC)

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Antioxidant vitamin intake and coronary mortality in a longitudinal population study.

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 Am J Epidemiol 1994 Jun 15;139(12):1180-9

Oxidation of lipoproteins is hypothesized to promote atherosclerosis and, thus, a high intake of antioxidant nutrients may protect against coronary heart disease. The relation between the intakes of dietary carotene, vitamin C, and vitamin E and the subsequent coronary mortality was studied in a cohort of 5,133 Finnish men and women aged 30-69 years and initially free from heart disease. Food consumption was estimated by the dietary history method covering the total habitual diet during the previous year. Altogether, 244 new fatal coronary heart disease cases occurred during a mean follow-up of 14 years beginning in 1966-1972. An inverse association was observed between dietary vitamin E intake and coronary mortality in both men and women with relative risks of 0.68 (p for trend = 0.01) and 0.35 (p for trend < 0.01), respectively, between the highest and lowest tertiles of the intake. Similar associations were observed for the dietary intake of vitamin C and carotenoids among women and for the intake of important food sources of these micronutrients, i.e., of vegetables and fruits, among both men and women. The associations were not attributable to confounding by major nondietary risk factors of coronary heart disease, i.e., age, smoking, serum cholesterol, hypertension, or

relative weight. The results support the hypothesis that antioxidant vitamins protect against coronary heart disease, but it cannot be excluded that foods rich in these micronutrients also contain other constituents that provide the protection.



Vitamin B-12, vitamin B-6, and folate nutritional status in men with hyperhomocysteinemia.

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Am J Clin Nutr 1993 Jan;57(1):47-53

We measured the vitamin B-6, vitamin B-12, and folic acid nutritional status in a group of apparently healthy men (n = 44) with moderate hyperhomocysteinemia (plasma homocysteine concentration > 16.3 $\mu\text{mol/L}$). Compared with control subjects (n = 274) with normal plasma homocysteine (< or = 16.3 $\mu\text{mol/L}$) concentrations, significantly lower plasma concentrations of pyridoxal-5'-phosphate (P < 0.001), cobalamin (P < 0.001), and folic acid (P = 0.004) were demonstrated in hyperhomocysteinemic men. The prevalence of suboptimal vitamin B-6, B-12, and folate status in men with hyperhomocysteinemia was 25.0%, 56.8%, and 59.1%, respectively. In a placebo-controlled follow-up study, a daily vitamin supplement (10 mg pyridoxal, 1.0 mg folic acid, 0.4 mg cyanocobalamin) normalized elevated plasma homocysteine concentrations within 6 wk. Because hyperhomocysteinemia is implicated as a risk factor for premature occlusive vascular disease, appropriate vitamin therapy may be both efficient and cost-effective to control elevated plasma homocysteine concentrations.



Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis.

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N Engl J Med 1995 Feb 2;332(5):286-91

BACKGROUND. Epidemiologic studies have identified hyperhomocysteinemia as a possible risk factor for atherosclerosis. We determined the risk of carotid-artery atherosclerosis in relation to both plasma homocysteine concentrations and nutritional determinants of hyperhomocysteinemia.

METHODS. We performed a cross-sectional study of 1041 elderly subjects (418 men and 623 women; age range, 67 to 96 years) from the Framingham Heart Study. We examined the relation between the maximal degree of stenosis of the extracranial carotid arteries (as assessed by ultrasonography) and plasma homocysteine concentrations, as well as plasma concentrations and intakes of vitamins involved in homocysteine metabolism, including folate, vitamin B12, and vitamin B6. The subjects were classified into two categories according to the findings in the more diseased of the two carotid vessels: stenosis of 0 to 24 percent and stenosis of 25 to 100 percent.

RESULTS. The prevalence of carotid stenosis of > or = 25 percent was 43 percent in the men and 34 percent in the women. The odds ratio for stenosis of > or = 25 percent was 2.0 (95 percent confidence interval, 1.4 to 2.9) for subjects with the highest plasma homocysteine concentrations (> or = 14.4 $\mu\text{mol per liter}$) as compared with those with the lowest concentrations (< or = 9.1 $\mu\text{mol per liter}$), after adjustment for sex, age, plasma high-density lipoprotein cholesterol concentration, systolic blood pressure, and smoking status (P < 0.001 for trend). Plasma concentrations of folate and pyridoxal-5'-phosphate (the coenzyme form of vitamin B6) and the level of folate intake were inversely associated with carotid-artery stenosis after adjustment for age, sex, and other risk factors.

CONCLUSIONS. High plasma homocysteine concentrations and low concentrations of folate and vitamin B6, through their role in homocysteine metabolism, are associated with an increased risk of extracranial carotid-artery stenosis in the elderly.



Vitamin requirements for the treatment of hyperhomocysteinemia in humans.

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J Nutr 1994 Oct;124(10):1927-33

We have previously shown that a modest vitamin supplement containing folic acid, vitamin B-12 and vitamin B-6 is effective in

reducing elevated plasma homocysteine concentrations. The effect of supplementation of the individual vitamins on moderate hyperhomocysteinemia has now been investigated in a placebo-controlled study. One hundred men with hyperhomocysteinemia were randomly assigned to five groups and treated with a daily dose of placebo, folic acid (0.65 mg), vitamin B-12 (0.4 mg), vitamin B-6 (10 mg) or a combination of the three vitamins for 6 wk. Folic acid supplementation reduced plasma homocysteine concentrations by 41.7% ($P < 0.001$), whereas the daily vitamin B-12 supplement lowered homocysteine concentrations by 14.8% ($P < 0.01$). The daily pyridoxine dose did not reduce significantly plasma homocysteine concentrations. The combination of the three vitamins reduced circulating homocysteine concentrations by 49.8%, which was not significantly different ($P = 0.48$) from the reduction achieved by folate supplementation alone. Our results indicate that folate deficiency may be an important cause of hyperhomocysteinemia in the general population.



Serum carotenoids and coronary heart disease. The Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study.

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JAMA 1994 Nov 9;272(18):1439-41

OBJECTIVE--To examine the relationship between total serum carotenoid levels and the risk of subsequent coronary heart disease (CHD) events.

DESIGN--New analysis of a cohort from the Lipid Research Clinics Coronary Primary Prevention Trial and Follow-up Study (LRC-CPPT). The LRC-CPPT was a multicenter placebo-controlled trial of cholestyramine resin and CHD with a follow-up period of 13 years. Serum carotenoids were measured at baseline.

PARTICIPANTS--The placebo group of the LRC-CPPT, which consisted of 1899 men aged 40 to 59 years with type II-a hyperlipidemia and without known preexisting CHD, cancer, or other major illnesses.

MAIN OUTCOME MEASURES--Nonfatal myocardial infarctions and deaths attributable to CHD ascertained from hospital records, autopsy reports, and death certificates and reviewed by a panel of cardiologists.

RESULTS--After adjustment for known CHD risk factors including smoking, serum carotenoids were inversely related to CHD events. Men in the highest quartile of serum carotenoids had an adjusted relative risk (RR) of 0.64 (95% confidence interval [CI], 0.44 to 0.92) compared with the lowest quartile. For men who never smoked, this RR was 0.28 (95% CI, 0.11 to 0.73).

CONCLUSIONS--The LRC-CPPT participants with higher serum carotenoid levels had a decreased risk of incident CHD. This finding was stronger among men who never smoked.



Double-blind trial of vitamin C in elderly hypertensives.

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J Hum Hypertens 1993 Aug;7(4):403-5

No abstract.



Effect of combined supplementation with alpha-tocopherol, ascorbate, and beta carotene on low-density lipoprotein oxidation.

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Circulation 1993 Dec;88(6):2780-6

BACKGROUND. Data continue to accumulate supporting a proatherogenic role for oxidized low-density lipoprotein (Ox-LDL).

Antioxidant micronutrients such as ascorbate, alpha-tocopherol, and beta carotene, levels of which can be favorably manipulated by dietary measures without side effects, could be a safe approach in inhibiting LDL oxidation. In fact, in vitro studies have shown that all three antioxidants can inhibit LDL oxidation. The present study was undertaken to ascertain both the safety and antioxidant effect of combined supplementation with alpha-tocopherol, ascorbate, and beta carotene on LDL oxidation.

METHODS AND RESULTS. The effect of combined supplementation with alpha-tocopherol (800 IU/d) plus ascorbate (1.0 g/d) and beta carotene (30 mg/d) on copper-catalyzed LDL oxidation was tested in a randomized, placebo-controlled study in two groups of 12 male subjects over a 3-month period. Blood samples for the lipoprotein profile, antioxidant levels, and LDL isolation were obtained at baseline and at 3 months. Neither placebo nor combined antioxidant therapy resulted in any side effects or exerted an adverse effect on the plasma lipoprotein profile. Compared with placebo, combined antioxidant therapy resulted in a significant increase in plasma ascorbate and lipid standardized alpha-tocopherol and beta carotene levels (2.6-, 4.1-, and 16.3-fold, respectively). At baseline, there were no significant differences in the time course curves and kinetics of LDL oxidation as evidenced by the thiobarbituric acid reacting substances (TBARS) assay and the formation of conjugated dienes. However, at 3 months, combined supplementation resulted in a twofold prolongation of the lag phase and a 40% decrease in the oxidation rate. The combined antioxidant group was also compared with a group that received 800 IU of alpha-tocopherol only. Although the combined antioxidant group had significantly higher ascorbate and beta carotene levels than the group supplemented with alpha-tocopherol alone, there were no significant differences between the two groups with respect to LDL oxidation kinetics.

CONCLUSIONS. Combined supplementation with ascorbate, beta carotene, and alpha-tocopherol is not superior to high-dose alpha-tocopherol alone in inhibiting LDL oxidation. Hence, alpha-tocopherol therapy should be favored in future coronary prevention trials involving antioxidants.



A comparison of the efficacy and toxic effects of sustained- vs immediate-release niacin in hypercholesterolemic patients.

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JAMA 1994 Mar 2;271(9):672-7

OBJECTIVE--To compare escalating doses of immediate-release (IR) and sustained-release (SR) niacin for effectiveness in reducing levels of low-density lipoprotein cholesterol and triglycerides and increasing levels of high-density lipoprotein cholesterol, and for the occurrence of adverse reactions, especially hepatotoxicity.

DESIGN--Randomized, double-blind, parallel comparison of IR and SR niacin administered sequentially at 500, 1000, 1500, 2000, and 3000 mg/d, each for 6 weeks.

SETTING--Cholesterol research center.

PATIENTS--Forty-six adults, 23 in each group, with low-density lipoprotein cholesterol levels greater than 4.14 mmol/L (160 mg/dL) after 1 month of a step 1 National Cholesterol Education Program diet.

OUTCOME MEASURES--Fourteen-hour fasting lipid and lipoprotein cholesterol levels, results of clinical laboratory tests, a symptom questionnaire, and withdrawal rates.

RESULTS--The SR niacin lowered low-density lipoprotein cholesterol levels significantly more than IR niacin did at the dosage of 1500 mg/d and above, while IR niacin increased high-density lipoprotein cholesterol levels significantly more than SR niacin did at all dosage levels. The reduction in triglyceride levels was similar with IR and SR niacin. Nine (39%) of the 23 patients assigned to the IR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were vasodilatory symptoms, fatigue, and acanthosis nigricans. Eighteen (78%) of the 23 patients assigned to the SR dosage form withdrew before completing the 3000-mg daily dose; the most common reasons for withdrawal were gastrointestinal tract symptoms, fatigue, and increases in levels of liver aminotransferases, often with symptoms of hepatic dysfunction. None of the patients taking IR niacin developed hepatotoxic effects, while 12 (52%) of the 23 patients taking SR niacin did.

CONCLUSION--The SR form of niacin is hepatotoxic and should be restricted from use. The IR niacin is preferred for the management of hypercholesterolemia but can also cause significant adverse effects and should be given only to patients who can be carefully monitored by experienced health professionals.



Thiamin status, diuretic medications, and the management of congestive heart failure.

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J Am Diet Assoc 1995 May;95(5):541-4

OBJECTIVE: To assess the prevalence of thiamin deficiency in patients with congestive heart failure who are treated with diuretics that inhibit sodium and chloride reabsorption in the thick ascending limb of the loop of Henle (loop diuretic therapy).

DESIGN: A cross-sectional investigation of thiamin status of consecutive patients with congestive heart failure being treated with loop diuretic therapy.

SETTING: Cardiology clinic of a midwestern tertiary-care medical center.

SUBJECTS: Thirty-eight patients were recruited (mean age +/- standard deviation = 55 +/- 14 years). Validation of methodology was conducted with nine age-matched control subjects.

MAIN OUTCOME MEASURES: Thiamin status was assessed biochemically by in vitro erythrocyte transketolase activity assay. Assessment of dietary intake of thiamin was accomplished with a semiquantitative food frequency questionnaire.

STATISTICAL ANALYSES PERFORMED: Fisher's exact test and logistic regression were used to evaluate relationships between thiamin status and variables of interest.

RESULTS: Biochemical evidence of thiamin deficiency was found in 8 of 38 (21%) patients. Evidence of risk for dietary thiamin inadequacy was found in 10 of 38 patients (25%). Seven of the 8 patients with biochemical evidence of thiamin deficiency met study criteria for dietary adequacy, although quantified data suggested that only 4 of the patients achieved two thirds of the Recommended Dietary Allowance. Biochemical evidence of thiamin deficiency tended to be more common among patients with poor left ventricular ejection fractions ($P = .07$).

CONCLUSIONS: Thiamin deficiency may occur in a substantial proportion of patients with congestive heart failure, and dietary inadequacy may contribute to increased risk.



Effect of vitamin E and beta carotene on the incidence of angina pectoris. A randomized, double-blind, controlled trial.

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JAMA 1996 Mar 6;275(9):693-8
Published erratum appears in JAMA 1998 May 20;279(19):1528

OBJECTIVE: To examine the effect of supplementation with vitamin E (alpha tocopherol), beta carotene, or both on the incidence of angina pectoris in men without known previous coronary heart disease.

DESIGN: Randomized, double-blind, placebo-controlled trial.

SETTING AND PARTICIPANTS: Participants in the Alpha Tocopherol, Beta Carotene Cancer Prevention Study (N=29133) were male smokers aged 50 through 69 years who were living in southern and western Finland. Of these men, 22269 were considered free of coronary heart disease at baseline and were followed up for the incidence of angina pectoris.

INTERVENTION: Participants were randomized to receive 50 mg/d of alpha tocopherol, 20 mg/d of beta carotene, both, or placebo in a 2x2 design.

OUTCOME MEASURES: An incident case was defined as the first occurrence of typical angina pectoris identified in administering the annually repeated World Health Organization (Rose) Chest Pain Questionnaire.

RESULTS: During a median follow-up time of 4.7 years (96427 person-years), 1983 new cases of angina pectoris were detected. Comparing alpha tocopherol-supplemented subjects with non-alpha tocopherol-supplemented subjects showed a relative risk (RR) of angina pectoris incidence of 0.91 (95% confidence interval[CI], 0.83 to 0.99; P=.04). The RR for incidence of angina pectoris for the beta carotene- supplemented subjects compared with those not receiving beta carotene was 1.06 (95% CI, 0.97 to 1.16; P=.19). Compared with those receiving placebo, the RRs for incidence of angina pectoris were 0.97 (95% CI, 0.85 to 1.10) and 0.96 (95% CI, 0.85 to 1.09) in the alpha tocopherol and alpha tocopherol plus beta carotene groups, respectively, and 1.13 (95% CI, 1.00 to 1.27) in the beta carotene group (P=.06). Baseline dietary intakes and serum levels of alpha tocopherol and beta carotene did not predict incidence of angina pectoris.

CONCLUSIONS: Supplementation with alpha tocopherol was associated with only a minor decrease in the incidence of angina pectoris. Beta carotene had no preventive effect and was associated with a slight increase of angina.



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

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Lancet 1996 Mar 23;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.



Ascorbic acid and plasma lipids.

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Epidemiology 1994 Jan;5(1):19-26

We examined the association between plasma lipids and total ascorbic acid in 256 men and 221 women age 20-65 years. Among men, we observed that high-density lipoprotein (HDL) cholesterol was 2.1 mg per dl higher, total:HDL cholesterol was 5.4% lower, total cholesterol was 4.8 mg per dl lower, low-density lipoprotein (LDL) cholesterol was 5.6 mg per dl lower, and triglyceride was 5.2% lower for each 0.5 mg per dl increment in ascorbic acid. The association between ascorbic acid and total:HDL cholesterol ratio in men was modified by glucose concentration. Among women, we observed that HDL cholesterol was 14.9 mg per dl higher for women with ascorbic acid levels ≤ 1.05 mg per dl and 0.9 mg per dl lower for women with ascorbic acid levels > 1.05 mg per dl for each 0.5 mg per dl increment in ascorbic acid. Total:HDL cholesterol ratio was 10.9% lower for women with ascorbic acid concentrations ≤ 1.45 mg per dl and 0.6% higher for women with ascorbic acid concentrations > 1.45 mg per dl for each 0.5 mg per dl increment. The associations among ascorbic acid concentration, total and LDL cholesterol, and triglyceride

concentrations were weak or absent among women. These results are consistent with earlier observations relating ascorbic acid and HDL cholesterol and indicate that ascorbic acid might also be related to total and LDL cholesterol concentrations in men.



Flavonoid intake and coronary mortality in Finland: a cohort study.

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BMJ 1996 Feb 24;312(7029):478-81

OBJECTIVE: To study the association between dietary intake of flavonoids and subsequent coronary mortality.

DESIGN: A cohort study based on data collected at the Finnish mobile clinic health examination survey from 1967-72 and followed up until 1992.

SETTINGS: 30 communities from different parts of Finland.

SUBJECTS: 5133 Finnish men and women aged 30-69 years and free from heart disease at baseline.

MAIN OUTCOME MEASURE: Dietary intake of flavonoids, total mortality, and coronary mortality.

RESULTS: In women a significant inverse gradient was observed between dietary intake of flavonoids and total and coronary mortality. The relative risks between highest and lowest quarters of flavonoid intake adjusted for age, smoking, serum cholesterol concentration, blood pressure, and body mass index were 0.69 (95% confidence interval 0.53 to 0.90) and 0.54 (0.33 to 0.87) for total and coronary mortality, respectively. The corresponding values for men were 0.76 (0.63 to 0.93) and 0.78 (0.56 to 1.08), respectively. Adjustment for intake of antioxidant vitamins and fatty acids weakened the associations for women; the relative risks for coronary heart disease were 0.73 (0.41 to 1.32) and 0.67 (0.44 to 1.00) in women and men, respectively. Intakes of onions and apples, the main dietary sources of flavonoids, presented similar associations. The relative risks for coronary mortality between highest and lowest quarters of apple intake were 0.57 (0.36 to 0.91) and 0.81 (0.61 to 1.09) for women and men, respectively. The corresponding values for onions were 0.50 (0.30 to 0.82) and 0.74 (0.53 to 1.02), respectively.

CONCLUSIONS: The results suggest that people with very low intakes of flavonoids have higher risks of coronary disease.



Usefulness of antioxidant vitamins in suspected acute myocardial infarction (the Indian experiment of infarct survival-3).

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Heart Research Laboratory, Medical Hospital and Research Centre, Moradabad, India.
Am J Cardiol 1996 Feb 1;77(4):232-6

In a randomized, double-blind, placebo-controlled trial, the effects of combined treatment with the antioxidant vitamins A (50,000 IU/day), vitamin C (1,000 mg/day), vitamin E (400 mg/day), and beta-carotene (25 mg/day) were compared for 28 days in 63 (intervention group) and 62 (placebo group) patients with suspected acute myocardial infarction. After treatment with antioxidants, the mean infarct size (creatinine kinase and creatine kinase-MB gram equivalents) was significantly less in the antioxidant group than in the placebo group. Serum glutamic-oxaloacetic transaminase decreased by 45.6 IU/dl in the antioxidant group versus 25.8 IU/dl in the placebo group ($p < 0.02$). Cardiac enzyme lactate dehydrogenase increased slightly (88.6 IU/dl) in the antioxidant group compared with that in the placebo group (166.5 IU/dl) ($p < 0.01$). QRS score in the electrocardiogram was significantly less in the antioxidant than in the placebo group. The following levels increased in the antioxidant group versus the placebo group, respectively: plasma levels of vitamin E increased by 8.8 and 2.2 $\mu\text{mol/L}$ ($p < 0.01$), vitamin C increased by 12.6 and 4.2 $\mu\text{mol/L}$ ($p < 0.01$), beta-carotene increased by 0.28 and 0.06 $\mu\text{mol/L}$ ($p < 0.01$), and vitamin A increased by 0.36 and 0.12 $\mu\text{mol/L}$ ($p < 0.01$). Serum lipid peroxides decreased by 1.22 pmol/ml in antioxidant versus 0.22 pmol/ml in the placebo group ($p < 0.01$). Angina pectoris, total arrhythmias, and poor left ventricular function occurred less often in the antioxidant group. Cardiac end points were significantly less in the antioxidant group (20.6% vs 30.6%, respectively). These results suggest that combined treatment with antioxidant vitamins A, E, C, and beta-carotene in patients with recent acute myocardial infarction may be protective against cardiac necrosis and oxidative stress, and could be beneficial in preventing complications and cardiac event rate in such patients.

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.

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Am J Clin Nutr 1996 Aug;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.

Homocysteine metabolism and risk of myocardial infarction: relation with vitamins B6, B12, and folate.

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Am J Epidemiol 1996 May 1;143(9):845-59

Elevated plasma homocyst(e)ine levels are an independent risk factor for vascular disease. In a case-control study, the authors studied the associations of fasting plasma homocyst(e)ine and vitamins, which are important cofactors in homocysteine metabolism, with the risk of myocardial infarction. The cases were 130 Boston area patients hospitalized with a first myocardial infarction and 118 population controls, less than 76 years of age, enrolled in 1982 and 1983. Dietary intakes of vitamins B6, B12, and folate were estimated from a food frequency questionnaire. After adjusting for sex and age, the authors found that the geometric mean plasma homocyst(e)ine level was 11% higher in cases compared with controls ($p = 0.006$). There was no clear excess of cases with extremely elevated levels. The age- and sex-adjusted odds ratio for each 3- $\mu\text{mol/liter}$ (approximately 1 standard deviation) increase in plasma homocyst(e)ine was 1.35 (95% confidence interval 1.05-1.75; p trend = 0/007). After further control for several risk factors, the odds ratio was not affected, but the confidence interval was wider and the p value for trend was less significant. Dietary and plasma levels of vitamin B6 and folate were lower in cases than in controls, and these vitamins were inversely associated with the risk of myocardial infarction, independently of other potential risk factors. Vitamin B12 showed no clear association with myocardial infarction, although methylmalonic acid levels were significantly higher in cases. Comparing the mean levels of several homocysteine metabolites among cases and controls, the authors found that impairment of remethylation of homocyst(e)ine (dependent of folate and vitamin B12 rather than on vitamin B6-dependent transsulfuration) was the predominant cause of high homocyst(e)ine levels in cases. Accordingly, plasma folate and, to a lesser extent, plasma vitamin B12, but not vitamin B6, correlated inversely with plasma homocyst(e)ine, even for concentrations at the high end of normal values. These data provide further evidence that plasma homocyst(e)ine is an independent risk factor for myocardial infarction. In this population, folate was the most important determinant of plasma homocyst(e)ine, even in subjects with apparently adequate nutritional status of this vitamin.

Vitamin supplementation and other variables affecting serum homocysteine and methylmalonic acid concentrations in elderly men and women.

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J Am Coll Nutr 1996 Aug;15(4):364-76

OBJECTIVE: An elevated serum concentration of the metabolite, homocysteine (Hcys): 1) can indicate folate or vitamin B12 deficiency, 2) is an independent risk factor for vascular disease. The metabolite, methylmalonic acid (MMA), is elevated in deficiency of vitamin B12, but not folate. The purpose of this study was to determine the effect of self-selected vitamin supplementation and other variables on serum Hcys and MMA concentrations in elderly men and women.

METHODS: Serum concentrations of Hcys, MMA, folate and vitamin B12 were measured for elderly volunteers, age 68-96 years, and compared for those consuming (26 men, 25 women) and not consuming (24 men, 25 women) self-selected vitamin supplements.

RESULTS: Compared with the nonsupplemented group, the supplemented group had lower mean serum MMA (208 +/- 162 vs. 241 +/- 98 nmol/L [\pm SD]) and Hcys (9.5 +/- 2.6 vs. 11.2 +/- 2.7 μ mol/L); and higher serum vitamin B12 (391 +/- 174 vs 292 +/- 107 pmol/L), and serum folate (46 +/- 15 vs. 24 +/- 10 nmol/L) $p < 0.05$. Among all 100 subjects, the prevalence of serum vitamin B12 < 221 pmol/L (300 pg/mL) was 18; MMA > 271 nmol/L, 16; Hcys > 16.2 μ mol/L, 3; folate < 5.0 nmol/L, none. Based on serum vitamin B12 < 221 nmol/L with elevated serum MMA, vitamin B12 deficiency was probable in seven subjects, of whom two were supplemented. All three subjects with elevated serum Hcys had elevated serum MMA as well, suggesting vitamin B12 deficiency or renal insufficiency. A stepwise linear regression model for serum Hcys explained 61.7% of the variance, and included (in order) serum creatinine, folate, vitamin B12, albumin, age and body mass index (BMI). A model with serum MMA replacing serum vitamin B12 explained 64.1% of the variance in serum Hcys. Folate did not enter the model for supplemented subjects, supporting a "threshold effect": serum Hcys was inversely related to serum folate at lower serum folate (nonsupplemented subjects), but at higher serum folate (supplemented subjects), the relationship was flat. In supplemented subjects, serum Hcys was still related to vitamin B12 status, confirming that tissue deficiency of the vitamin was present.

CONCLUSIONS: Results showed potential usefulness of serum MMA and Hcys in identifying subclinical or tissue deficiency of vitamin B12. Clinicians should be aware of the risk of vitamin B12 deficiency in older people and of current screening algorithms using serum metabolites. These elderly volunteers had generally good folate status; nevertheless, some subjects seemed likely to benefit from an improvement in folate status that would reduce their serum Hcys within the normal range. The role of serum creatinine in the normal range in predicting serum Hcys, a vascular disease risk factor, remains unexplained.



Effectiveness of low-dose crystalline nicotinic acid in men with low high-density lipoprotein cholesterol levels.

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Arch Intern Med 1996 May 27;156(10):1081-8

BACKGROUND: Hypoalphalipoproteinemia (low serum concentration of high-density lipoprotein cholesterol [HDL-C]) is a common pattern of dyslipidemia associated with coronary heart disease. High doses of nicotinic acid effectively raise HDL-C levels in this condition, but they are commonly accompanied by side effects. The efficacy of low doses of nicotinic acid that may produce fewer side effects has not been adequately studied.

OBJECTIVE: To determine the effects of low-dose nicotinic acid on HDL-C levels in patients with hypoalphalipoproteinemia.

METHODS: Forty-four men with low HDL-C levels (< 1.03 mmol/L [< 40 mg/dL]) entered the study. Twenty-four patients otherwise had normal lipid levels, and 20 were moderately hypertriglyceridemic (range of plasma triglyceride levels, 2.82 to 5.64 mmol/L 250 to 500 mg/dL). The trial consisted of 3 phases; each phase lasted 8 weeks. The first phase was diet only (30% fat diet); in the second phase, crystalline nicotinic acid was added at 1.5 g/d; and in the third phase, the dose was increased to 3 g/d.

RESULTS: Of the 44 patients who entered the study, 37 completed the low-dose phase (1.5 g/d); the remaining patients were withdrawn because of side effects to nicotinic acid. Four other patients who completed the low-dose phase were excluded from the higher dose phase because of side effects that developed when they were receiving the low dose. Ten other patients withdrew during the high-dose phase because of side effects. In both groups, responses to nicotinic acid therapy tended to be dose-dependent. For both groups, the higher dose generally produced a greater reduction in apolipoprotein B-containing lipoproteins and a greater rise in HDL-C levels. However, for both groups, the low dose of nicotinic acid gave an average 20% increase in HDL-C levels.

CONCLUSIONS: A low dose (1.5 g/d) of crystalline nicotinic acid causes an average 20% increase in HDL-C levels and significantly lowers triglyceride levels in both normolipidemic and hyperlipidemic patients with low HDL-C levels. Although the changes induced by this dose are less than those that can be achieved by a higher dose, the lower dose is better tolerated. Nicotinic acid may be useful in combined drug therapy for secondary prevention of coronary heart disease, and if higher doses cannot be tolerated, use of

a lower dose should still be useful for producing a moderate rise in HDL-C levels in patients with hypoalphalipoproteinemia.



Plasma homocysteine levels and mortality in patients with coronary artery disease.

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N Engl J Med 1997 Jul 24;337(4):230-6

BACKGROUND: Elevated plasma homocysteine levels are a risk factor for coronary heart disease, but the prognostic value of homocysteine levels in patients with established coronary artery disease has not been defined.

METHODS: We prospectively investigated the relation between plasma total homocysteine levels and mortality among 587 patients with angiographically confirmed coronary artery disease. At the time of angiography in 1991 or 1992, risk factors for coronary disease, including homocysteine levels, were evaluated. The majority of the patients subsequently underwent coronary-artery bypass grafting (318 patients) or percutaneous transluminal coronary angioplasty (120 patients); the remaining 149 were treated medically.

RESULTS: After a median follow-up of 4.6 years, 64 patients (10.9 percent) had died. We found a strong, graded relation between plasma homocysteine levels and overall mortality. After four years, 3.8 percent of patients with homocysteine levels below 9 micromol per liter had died, as compared with 24.7 percent of those with homocysteine levels of 15 micromol per liter or higher. Homocysteine levels were only weakly related to the extent of coronary artery disease but were strongly related to the history with respect to myocardial infarction, the left ventricular ejection fraction, and the serum creatinine level. The relation of homocysteine levels to mortality remained strong after adjustment for these and other potential confounders. In an analysis in which the patients with homocysteine levels below 9 micromol per liter were used as the reference group, the mortality ratios were 1.9 for patients with homocysteine levels of 9.0 to 14.9 micromol per liter, 2.8 for those with levels of 15.0 to 19.9 micromol per liter, and 4.5 for those with levels of 20.0 micromol per liter or higher (P for trend=0.02). When death due to cardiovascular disease (which occurred in 50 patients) was used as the end point in the analysis, the relation between homocysteine levels and mortality was slightly strengthened.

CONCLUSIONS: Plasma total homocysteine levels are a strong predictor of mortality in patients with angiographically confirmed coronary artery disease.



Vitamin C deficiency and risk of myocardial infarction: prospective population study of men from eastern Finland.

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Research Institute of Public Health, University of Kuopio, Finland.

BMJ 1997 Mar 1;314(7081):634-8

OBJECTIVE: To examine the association between plasma vitamin C concentrations and the risk of acute myocardial infarction.

DESIGN: Prospective population study.

SETTING: Eastern Finland.

SUBJECTS: 1605 randomly selected men aged 42, 48, 54, or 60 who did not have either symptomatic coronary heart disease or ischaemia on exercise testing at entry to the Kuopio ischaemic heart disease risk factor study in between 1984 and 1989.

MAIN OUTCOME MEASURES: Number of acute myocardial infarctions; fasting plasma vitamin C concentrations at baseline.

RESULTS: 70 of the men had a fatal or non-fatal myocardial infarction between March 1984 and December 1992. 91 men had vitamin C deficiency (plasma ascorbate < 11.4 $\mu\text{mol/l}$, or 2.0 mg/l), of whom 12 (13.2%) had a myocardial infarction; 1514 men were not deficient in vitamin C, of whom 58 (3.8%) had a myocardial infarction. In a Cox proportional hazards model adjusted for age, year of examination, and season of the year examined (August to October v rest of the year) men who had vitamin C deficiency had a relative risk of acute myocardial infarction of 3.5 (95% confidence interval 1.8 to 6.7, $P = 0.0002$) compared with those who were not deficient. In another model adjusted additionally for the strongest risk factors for myocardial infarction and for dietary

intakes of tea fibre, carotene, and saturated fats men with a plasma ascorbate concentration < 11.4 $\mu\text{mol/l}$ had a relative risk of 2.5 (1.3 to 5.2, $P = 0.0095$) compared with men with higher plasma vitamin C concentrations.

CONCLUSIONS: Vitamin C deficiency, as assessed by low plasma ascorbate concentration, is a risk factor for coronary heart disease.



Vitamin C status and blood pressure.

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Institute of Public Health, University Forvie Site, Cambridge, UK.
J Hypertens 1996 Apr;14(4):503-8

OBJECTIVE: To examine the cross-sectional relationship between blood pressure and plasma vitamin C.

DESIGN: A cross-sectional analysis.

SETTING: A population-based study.

SUBJECTS: The subjects were 835 men and 1025 women aged 45-75 years registered with general practices in Norfolk.

INTERVENTIONS: Completion of health and lifestyle questionnaire and attendance for a health check.

MAIN OUTCOME MEASURES: Diastolic blood pressure (DBP), systolic blood pressure (SBP) and plasma vitamin C level.

RESULTS: The mean SBP was 135.8 \pm 18.5 mmHg (mean \pm SD) and the mean DBP was 82.5 \pm 11.3 mmHg. The mean plasma vitamin C level was 52.6 \pm 19.7 $\mu\text{mol/l}$. The plasma vitamin C level was negatively correlated both with SBP and with DBP. These correlations persisted after adjustment for age, sex and body mass index. Adjusting for other confounders including cigarette smoking, physical activity and alcohol intake did not alter the observed association. Exclusion of subjects taking vitamin supplements and those with known hypertension did not affect the results. The differences in SBP and in DBP for a 50 $\mu\text{mol/l}$ difference in vitamin C, estimated using linear regression, were -3.6 and -2.6 mmHg, respectively.

CONCLUSIONS: The plasma vitamin C level may be a marker of other factors; nevertheless, these results are consistent with other published work indicating that a high intake of vitamin C from food confers protection against raised blood pressure and strokes.



Amphiphilic alpha-tocopherol analogues as inhibitors of brain lipid peroxidation.

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Eur J Pharmacol (Netherlands) Feb 29 1996, 298 (1) p37-43

Neurological disorders, such as stroke, trauma, tardive dyskinesia, Alzheimer's and Parkinson's diseases, may be partially attributed to excessive exposition of the nervous tissue to oxygen-derived radicals. A novel water-soluble alpha-tocopherol analogue, 2,3-dihydro-2,2,4,6,7-pentamethyl-3-methylpiperazino methyl-1-benzofuran-5-ol dihydrochloride (MDL), is a potent radical scavenger. Following subcutaneous administration to mice, MDL inhibited the lipid peroxidation induced in the 100-fold diluted brain homogenates, with an ID₅₀ of 8 mg/kg. Rapid brain penetration, within 30-60 min postadministration, and even distribution into different brain areas were observed. MDL was also detected after oral administration. In brain homogenate undergoing lipid peroxidation, MDL prevented the consumption of an equal amount of alpha-tocopherol, while inhibiting the concomitant malondialdehyde formation. The radical scavenging capacity of MDL was superior to that of alpha-tocopherol, although the peak and half-peak potentials were not significantly different. However, MDL was much less lipophilic, the partition coefficient (log P) at the octanol/water interface being 1.91. Although it is yet unknown, whether the applied criteria sufficiently predict its usefulness, beneficial effects of MDL may be expected in the above mentioned disorders.



[Effect of piracetam on inorganic phosphates and phospholipids in the blood of patients with cerebral infarction in the earliest period of the disease]

Kawiak W, Pilarczyk M, Chmielewska B, Gieracz-Nazar A
Katedry i Kliniki Neurologii Akademii Medycznej, Lublinie.
Neurol Neurochir Pol 1991 Nov-Dec;25(6):731-6

The influence of piracetam on the level of inorganic and phospholipid phosphorus in blood of ischemic stroke patients was evaluated. In healthy patients piracetam (2G, i.v.) diminished the concentration of inorganic phosphorus and essentially lowered the content of ion connected with phospholipids. In stroke patients inorganic phosphorus was primarily enhanced and organic lowered. Treatment with piracetam lowered the concentration of both inorganic and phospholipid phosphorus in blood.



Effect of piracetam on recovery and rehabilitation after stroke: A double-blind, placebo-controlled study

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Speech and Language Therapy Research Unit, Frenchay Hospital, Bristol, England.
Clin. Neuropharmacol. (USA, 1994, 17/4 (320-331)

The nootropic agent piracetam has been shown to improve learning and memory, and it may, by this means, facilitate recovery and rehabilitation after a stroke. We report the results of a pilot study exploring its effects in patients undergoing rehabilitation after acute cerebral infarction in the carotid artery territory. We compared piracetam and placebo, each given for 12 weeks, in a multicenter, double-blind, randomized trial of parallel-group design; testing was performed at baseline (6-9 weeks poststroke), weeks 5 and 12, and, in fewer patients, 12 weeks after termination of treatment. Standardized tests of activities of daily living (Barthel Index, Kuriansky Test), aphasia (Aachen Aphasia Test), and perception (Rivermead Perception Assessment Battery) were the primary efficacy variables. Of 158 patients, 137 (81 males, 56 females) were studied after treatment and 88 at 24-week follow-up. Thirty patients on piracetam (45%) and 37 on placebo (53%) were aphasic on entry. Both groups, including the subgroups with aphasia, were well matched at baseline for demographic data, stroke sequelae, type and severity of aphasia, and prognostic parameters. Multivariate analysis of Aachen Aphasia subtest scores showed a significant overall improvement relative to baseline in favor of piracetam ($p = 0.02$) at 12 weeks. This was not seen at 24 weeks when, however, fewer patients were available for evaluation so that we could neither confirm nor deny whether improvement was maintained after cessation of piracetam. We were unable to demonstrate an effect on tests of activities of daily living and could neither confirm nor exclude an effect on perceptual deficit. We have shown an improvement in aphasia in patients undergoing rehabilitation after a stroke after 12 weeks' treatment with piracetam that requires confirmation in further studies.



Ergoloids (Hydergine) and ischaemic strokes; Efficacy and mechanism of action

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J Int Med Res 1995 May-Jun;23(3):154-66

In this double-blind, randomized study the efficacy of the ergoloid compounds, co-dergocrine mesylate and nicergoline, in the rehabilitation of patients with ischaemic stroke was investigated. A group of 30 patients was treated daily with 60 mg nicergoline, orally, and a second group of 27 patients was given 1.8-6 mg co-dergocrine mesylate, orally or intramuscularly, daily (depending on the time since the initial ischaemic insult) for 6 months. Outcome measures included: motoricity index (limb function); Sandoz Clinical Assessment Geriatric (SCAG) scale; psychometric tests to assess functions such as attention, psychomotor performance, perception and sensory and short-term memory; conventional and computerized electroencephalography; and P300 and reaction time measures. The results showed improvements in some aspects such as limb function ($P < 0.05$), SCAG score ($P < 0.01$) and some electrophysiological parameters ($P < 0.01$) after treatment with both drugs. Though statistically significant most of the changes were not large. The efficacy of both drugs was qualitatively similar. The quantitative difference in some aspects in favour of nicergoline could be attributed to differences in the mechanisms of action of the two drugs, although it is also possible that the difference may reflect the dosages used. Nootropic drugs may induce a condition that facilitates the effects of cognitive training.



Satellite symposium 'Piracetam and acute stroke : Pass' within the framework of the 3rd

International Conference on stroke, 18-21 October 1995 in Prague

Soyka D.
Nervenheilkunde (Germany, 1996, 15/1)

No abstract.



The nootropic agent piracetam in the treatment of acute stroke

[No author listed]
TW Neurologie Psychiatrie (Germany, 1996, 10/1-2 (81))

No abstract.



Cerebroprotective effect of piracetam: The acute and chronic administrations of piracetam during short-term and long-term transient ischaemia

Kurtdede N.; Ercakir M.; Gurer Y.; Asti R.N.; Gurer F.; Acikalin E.; Unal N.; Tanyolac A.
Turkish Journal of Medical Sciences (Turkey), 1995, 24/SUPPL.(39)

No abstract.



Putaminal and thalamic hemorrhage in ethnic chinese living in Hong Kong.

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Department of Surgery, Prince of Wales Hospital, Chinese University of Hong Kong.
Surg Neurol (United States) Nov 1996, 46 (5) p441-5

BACKGROUND: Hemorrhagic stroke is very common in the Chinese population, and it is one of the leading causes of mortality in Chinese communities. The risk factors to explain this high incidence are unknown. It is the purpose of this study to look into the features of hemorrhagic stroke in the Hong Kong Chinese.

METHODS: We conducted a prospective hospital-based study in which 60 consecutive Chinese patients with computed tomography diagnosis of putaminal or thalamic hemorrhage were included. Their demographic and clinical data were collected and analyzed.

RESULTS: Two major findings evolved from the present study.

(1) Unlike the Western studies, the majority of our patients were about a decade younger;

(2) 50% of the patients had previously diagnosed hypertension, but only 20% of these patients were compliant with their antihypertensive medication. Our results also suggested that low admission Glasgow Coma Scale scores, large hematoma size, and the presence of intraventricular blood were associated with poor outcomes.

CONCLUSIONS: This study concludes that hemorrhagic stroke is indeed a serious health problem in Hong Kong. Simple measures, such as improvement of health education and the primary care system in the management of hypertension, would help to reduce the incidence of hemorrhagic stroke.



Diet and heart disease. The role of fat, alcohol, and antioxidants.

Overwhelming evidence indicates that the Western diet plays a major role in atherogenesis. Clinicians are only now beginning to tease out the precise components of the diet that are harmful or beneficial. With respect to fat intake, it remains unclear whether it is the amount or type of fat that promotes atherosclerotic disease. There appears to be a consistent positive association of cholesterol, saturated fat, and possibly trans-fatty acid intake and atherosclerotic disease. Although there is general agreement that reducing intake of these dietary components would be beneficial, controversy remains on what should replace these harmful fats. Some researchers advocate massive reductions in total fat consumption with replacement with carbohydrates for everyone, whereas others recommend a Mediterranean-style diet, which replaces saturated animal fats with vegetable fats. Very low-fat diets have been shown to lower the chance of a heart attack among those with severe coronary artery disease, but for the majority of Americans who do not have obvious artery disease, there is no convincing evidence that a very low-fat diet is optimal. There may be other adverse health effects of this Asian diet, such as increased rates of hemorrhagic stroke. Further research is required to refine thinking on the optimal composition of fats in diet. The effects of alcohol consumption on chronic diseases are complex. The strength and consistency of the observational and experimental evidence strongly suggests a causal link between light to moderate alcoholic beverage consumption and reduced risks of CHD. These reductions in risk of CHD appear to be mediated largely by raising HDL cholesterol levels, although additional mechanisms remain possible and do not appear to be beverage specific. Maximal benefit in terms of CHD appears to be at the level of one drink per day. From a public policy standpoint, whether the benefits for CHD persist at heavy drinking levels or are attenuated is moot because clear harm of heavy drinking in terms of overexertion of heart disease. Although the association of alcohol and CHD is likely to be causal, any individual or public health recommendations must consider the complexity of alcohol's metabolic, physiologic, and psychological effects. With alcohol, the differences between daily intake of small to moderate and large quantities may be the difference between preventing and causing disease. A discussion of alcohol intake should be a part of routine preventive counseling. Given the complex nature of alcohol disease relationships, alcohol consumption should not be viewed as a primary preventive strategy; also, it should not necessarily be viewed as an unhealthy behavior. Based on the totality of available evidence, antioxidants represent a possible but as yet unproven means to reduce risks of cardiovascular disease. Although it remains unclear whether supplementation of diet with antioxidant vitamins will reduce risks of atherosclerotic disease, most researchers agree that consumption of fruits and vegetables is an important part of a healthy diet. The U.S. Department of Agriculture recommends two to four servings of fruit and three to five servings of vegetables per day. (130 Refs.)



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