

# Health Benefits of Nutritional Supplements

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*Selected Readings from the Last 23 Years (1990-2013)*

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## Foreword

The importance of nutrition for human health has long been recognized. Prior to 1960, interest in this field focused primarily 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, and essential fatty acids) were identified, and recommended daily intakes for those essential nutrients were developed. These recommendations, in turn, proved valuable in eradicating acute nutrient deficiency diseases.

During the past 23 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 well-known examples of diseases with dietary risk factors, and research is currently underway on many more nutrient-disease interactions. Unfortunately, these associations are difficult to study, in part because of the timeframes involved. Chronic degenerative diseases develop over decades (or lifetimes), and it is extremely difficult to conduct research programs spanning more than several years in length. Nevertheless, advances in epidemiological and clinical research have uncovered a great deal of information about the impact of diet and nutrient intakes on long-term health.

Over the past decade, science and healthcare researchers have paid increasing attention to the role of nutritional supplements as possible dietary components with roles in preventing and treating chronic disease. Hundreds of scientific studies have been conducted and published, each spanning a broad range of potential health issues. These studies have employed a wide variety of methodologies and they have

*"We recommend that all adults take one multivitamin daily. This practice is justified mainly by the known and suspected benefits of supplemental folic acid and vitamins B12, B6, and D in preventing cardiovascular disease, cancer, and osteoporosis..."*

*We recommend multivitamins, rather than individual vitamins, because multivitamins are simpler to take and cheaper than the individual vitamins taken separately and because a large proportion of the population needs supplements of more than one vitamin."*

*-Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. 2002. JAMA 287:3127-9.*

produced both positive and negative results. In some areas – such as the role of calcium and vitamin D supplements in slowing the progression of osteoporosis, or the role of folic acid supplements in preventing certain birth defects – results have been largely consistent, and these nutrients have become an accepted part of modern healthcare practices. In other areas (e.g. the role of antioxidant supplementation in preventing heart disease), results have been less consistent, and firm conclusions remain controversial.

The following is an enumerative bibliography of peer-reviewed research examining possible health benefits of nutritional supplements and functional foods. This list is not exhaustive. Papers have been selected on the basis of scientific merit and relevance to the field, regardless of whether positive or negative results were obtained. Our objective in compiling this list is to provide readers with a good cross-section of recent scientific literature, with hopes of contributing to a better understanding of the current state of nutritional research.

For convenience, references have been sorted by health issue:

- Cardiovascular Health
- Cancer
- Bone and Joint Health
- Healthy Pregnancies and Healthy Babies
- Immune Function
- Healthy Vision
- Other

*These statements have not been evaluated by the Food and Drug Administration. No USANA product is intended to diagnose, treat, cure, or prevent any disease.*

# Cardiovascular Health

1. Abbey M, Nestel PJ, Baghurst PA. Antioxidant vitamins and low-density-lipoprotein oxidation. 1993. *Am J Clin Nutr* 58(4):525-32.
2. Adank C, Green TJ, Skeaff CM, Briars B. Weekly high-dose folic acid supplementation is effective in lowering serum homocysteine concentrations in women. 2003. *Ann Nutr Metab* 47(2):55-9.
3. Allender PS, Cutler JA, Follmann D, Cappuccio FP, Pryer J, Elliott P. Dietary calcium and blood pressure: a meta-analysis of randomized clinical trials. 1996. *Ann Intern Med* 124(9):825-31.
4. Agarwal S, Rao AV. Tomato lycopene and low density lipoprotein oxidation: a human dietary intervention study. 1998. *Lipids* 33(10):981-4.
5. Aminbakhsh A, Mancini J. Chronic antioxidant use and changes in endothelial dysfunction: a review of clinical investigations. 1999. *Can J Cardiol* 15(8):895-903.
6. Anderson JW, Allgood LD, Lawrence A, Altringer LA, Jerdack GR, Hengehold DA, Morel JG. Cholesterol-lowering effects of psyllium intake adjunctive to diet therapy in men and women with hypercholesterolemia: meta-analysis of 8 controlled trials. 2000. *Am J Clin Nutr* 71(2):472-9.
7. Anderson JW, Davidson MH, Blonde L, Brown WV, Howard WJ, Ginsberg H, Allgood LD, Weingand KW. Long-term cholesterol-lowering effects of psyllium as an adjunct to diet therapy in the treatment of hypercholesterolemia. 2000. *Am J Clin Nutr* 71(6):1433-8.
8. Ascherio A, Rimm EB, Hernan MA, Giovannucci E, Kawachi I, Stampfer MJ, Willett WC. Relation of consumption of vitamin E, vitamin C, and carotenoids to risk for stroke among men in the United States. 1999. *Ann Intern Med* 130(12):963-70.
9. Bao B, Prasad AS, Beck FW, Fitzgerald JT, Snell D, Bao GW, Singh T, Cardozo LJ. Zinc decreases C-reactive protein, lipid peroxidation, and inflammatory cytokines in elderly subjects: a potential implication of zinc as an atheroprotective agent. 2010. *AJCN* 91:1634-41.
10. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. 2006. *Nat Rev Drug Discov* 5(6):493-506.

"Mg<sup>2+</sup> [magnesium] deficiency or a reduction in dietary intake of Mg<sup>2+</sup> plays an important role in the etiology of diabetes and numerous cardiovascular diseases including thrombosis, atherosclerosis, ischemic heart disease, myocardial infarction, hypertension, arrhythmias and congestive heart failure in humans. Mg<sup>2+</sup> supplementation can bring about a significant decrease in blood pressure and a stabilization of cardiac arrhythmias and acute myocardial infarction."

-S Chakraborti, et al. (#22)

"As indicated in Table 1, the 900 mg/day target for EPA/DHA could require 3-21 servings of fish/week depending upon the source/type chosen. Consequently, a high quality fish oil supplement/concentrate and functional foods enriched in EPA/DHA will become important vehicles for enhancing current low intakes of EPA/DHA..."

-DJ Holub, et al. (#66)

11. Bellamy MF, McDowell IF, Ramsey MW, Brownlee M, Newcombe RG, Lewis MJ. Oral folate enhances endothelial function in hyperhomocysteinaemic subjects. 1999. *Eur J Clin Invest* 29:659-62.
12. Berman M, ERman A, Ben-Gal T, Dvir D, Georgiou GP, Stamler A, Vered Y, Vidne BA, Aravot D. Coenzyme Q10 in patients with end-stage heart failure awaiting cardiac transplantation: a randomized, placebo-controlled study. 2004. *Clin Cardiol* 27(5):295-9.
13. Boaz M, Smetana S, Weinstein T, Matas Z, Gafer U, Iaina A, Knecht A, Weissgarten Y, Brunner D, Fainaru M, Green MS. Secondary prevention with antioxidants of cardiovascular disease in endstage renal disease (SPACE): randomized placebo-controlled trial. 2000. *Lancet* 356(9237):1213-8.
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15. Brouwer IA, van Dusseldorp M, Thomas CM, Duran M, Hautvast JG, Eskes TK, Steegers-Theunissen RP. Low-dose folic acid supplementation decreases plasma homocysteine concentration: a randomized trial. 1999. *Am J Clin Nutr* 69(1):99-104.
16. Brouwer IA, van Rooij IA, van Dusseldorp M, Thomas CM, Blom HJ, Hautvast JG, Eskes TK, Steegers-Theunissen RP. Homocysteine-lowering effect of 500 microg folic acid every other day versus 250 microg/day. 2000. *Ann Nutr Metab* 44(5-6):194-7.
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26. Collaborative Group of the Primary Prevention Project (PPP). Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. 2001. *Lancet* 357(9250):89-95.
27. Connor WE. Importance of n-3 fatty acids in health and disease. 2000. *Am J Clin Nutr* 71(suppl):171S-5S.

"Vitamin C, carotenoids, and vitamin E, the three main dietary sources of antioxidants, each affect lipid peroxidation and may reduce atherogenesis and lower the risk of coronary heart disease (CHD)."

-EB Rimm, et al. (#123)

"In this large prospective study of women, we observed a modest inverse association between intake of vitamin C and incidence of CHD [coronary heart disease]. Women in the highest quintile of vitamin C intake ( $\geq 360$  mg/day) from diet and supplements had a 27% lower risk of nonfatal MI and fatal CHD than women in the lowest quintile of intake ( $\leq 93$  mg/day). The reduction in risk appeared to be limited to women who took vitamin C supplements. Among users of vitamin C supplements, we observed a significant 28% lower risk of nonfatal MI and fatal CHD than among non-users. Although risk did not vary significantly according to duration of use of supplements or dose of supplements, the reduction in risk was somewhat stronger for women taking at least 400 mg/day."

-SK Osganian, et al. (#112)

28. Constans J, Blann AD, Resplandy F, Parrot F, Renard M, Seigneur M, Guerin V, Boisseau M, Conri C. Three months supplementation of hyperhomocysteinaemic patients with folic acid and vitamin B6 improves biological markers of endothelial dysfunction. 1999. *Br J Haematol* 107:776-8.
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41. Elliott TG, Barth JD, Mancini GB. Effects of vitamin E on endothelial function in men after myocardial infarction. 1995. *Am J Cardiol* 76(16):1188-90.

"The NHEFS findings are consistent with the hypothesis that high levels of antioxidant vitamins (such as vitamins C, E, and A) increase the body's defense system against free radicals and reduce the risk of arteriosclerosis. Furthermore, the NHEFS findings are plausible in the sense that they are consistent with the secular trends during the last 20 years of large increases in the consumption of supplements containing vitamin C and large declines in age-adjusted death rates (total, cardiovascular disease, and stomach cancer) in the general population that are only partially explained by established risk factors."

-JE Enstrom, et al. (#44)

"Overall, DHA supplementation reduced the concentrations of atherogenic lipids and lipoproteins and increased concentrations of cardioprotective lipoproteins."

-DS Kelley, et al. (#76)

42. Emmert DH, Kirchner JT. The role of vitamin E in the prevention of heart disease. 1999. *Arch Fam Med* 8(6):537-42.

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recipients. 1993. *J Am Coll Cardiol* 21:982-9.

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52. Gilligan DM, Sack MN, Guetta V, Casino PR, Quyyumi AA, Rader DJ, Panza JA, Cannon RO. Effect of antioxidant vitamins on low density lipoprotein oxidation and impaired endothelium-dependent vasodilation in patients with hypercholesterolemia. 1994. *J Am Coll Cardiol* 24(7):1611-7.

53. GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results from the GISSI-Prevenzione trial. 1999. *Lancet* 354:447-55.

54. Gillman MW, Hood MY, Moore LL, Nguyen US, Singer MR, Andon MB. Effect of calcium supplementation on blood pressure in children. 1995. *J Pediatr* 127(2):186-92.

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*"It appears that coenzyme Q10 may be of benefit in a variety of clinical situations. It may have a role in the prevention of cardiovascular disease because of its role in preventing LDL oxidation, though this role requires further research. It appears that this substance is deficient in many patients with a variety of cardiovascular disorders, and that some of them—particularly those with coronary artery disease, heart failure, and cardiomyopathy—may benefit from its ability to enhance the efficiency of myocardial energy production."*

-B Sarter (#130)

*"In mammals, there is growing evidence that resveratrol can prevent or delay the onset of cancer, heart disease, ischaemic and chemically induced injuries, diabetes, pathological inflammation and viral infection."*

-JA Baur, et al. (#10)

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infarction in men and women – Stockholm Heart Epidemiology Program (SHEEP). 2003. *J Nutr* 133(8):2650-4.

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*"In this study we demonstrated that higher intake of dietary linolenic acid was associated with a lower prevalence of CAC as measured by cardiac CT in both men and women, after adjustment for confounding factors, in a dose-response fashion. This association was independent of age, education, income, energy intake, ratio of n-6 to n-3 fatty acids, and fish consumption."*

*-L Djousse, et al. (#36)*

*"Supplemental CoQ10 alters the natural history of cardiovascular illnesses and has the potential for prevention of cardiovascular disease through the inhibition of LDL cholesterol oxidation and by the maintenance of optimal cellular and mitochondrial function throughout the ravages of time and internal and external stresses."*

*-PH Langsjoen, et al. (#83)*

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*-AT Merchant, et al. (#98)*

*"We conclude that CoQ10 administration can improve recovery of the mitochondrion and the cardiac myocyte from stress. When given for one week prior to surgery, CoQ10 can accelerate cardiac recovery and lead to earlier discharge of the patient from the hospital."*

*-FL Rosenfeldt, et al. (#126)*

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*"Polyunsaturated fatty acids (PUFAs) of the n-6 and n-3 series are essential nutrients that exert an important influence on plasma lipids and serve cardiac and endothelial functions to impact the prevention and treatment of coronary heart diseases (CHD). Both n-6 and n-3 PUFAs have distinct biological effects contributing to their cardioprotective action."*

-V Wijendran, et al. (#169)

*"In conclusion, our results showed that consumption of a calcium+D supplement enhanced the beneficial effect of body weight loss on the lipid and lipoprotein profile in overweight or obese women with usual low calcium intake... [In] the clinical context of obesity treatment, calcium supplementation could be recommended in women with inadequate calcium intake to improve the cardiovascular disease risk profile."*

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*"The administration of CoQ10 to heart transplant candidates led to a significant improvement in functional status, clinical symptoms, and quality of life."*

*-M Berman, et al. (#12)*

*"Several epidemiological studies have revealed an inverse relationship between vitamin E intake and the progression of chronic diseases. It is believed that vitamin E's various actions, including its role as an antioxidant, have both antiatherogenic effects and chemoprotective action."*

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"This review confirms the efficacy of Ginkgo biloba extract Egb 761. It demonstrates not only the statistical significance of the difference with respect to placebo but also the clinical relevance for the treatment of patients with PAOD [peripheral arterial occlusive disease]."

-S Horsch, et al. (#68)

"The combined cardiovascular effects of resveratrol and other plant phenolic compounds and bioflavonoids with vitamin E should also be encouraged. Finally, resveratrol should be evaluated as an interesting candidate for non-drug approaches to combat blood vessel-related diseases in humans."

-JM Wu, et al. (#176)



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*"In summary, the results of the present study suggest that moderate to severe vitamin D deficiency is a risk factor for developing cardiovascular disease. These findings may have potentially broad public health implications, given the high prevalence of vitamin D deficiency in developed countries, the contribution of lifestyle and geography to vitamin D status, and the ease, safety, and low cost of treating vitamin D deficiency."*

*-TJ Wang, et al. (#164)*

*"Evidence from prospective secondary prevention studies suggests that EPA/DHA supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality."*

*-PM Kris-Etherton, et al. (#79)*

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-HW Wilmink, et al. (#170)

# Cancer

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*"The results of this randomized controlled trial do not support the hypothesis that selenium supplementation reduces the risk of BCC or SCC of the skin, showing no statistically significant treatment effect on their incidence. However, selenium supplementation was found to be associated with significant reductions in secondary end points of total cancer incidence (all-sites combined), long, colorectal and prostate cancer incidences, and lung cancer mortality."*

- LC Clark, et al. (#199)

*"In vitro, animal and clinical studies strongly indicate that vitamin D may have anticancer benefits, including against progression (such as metastasis) in colorectal cancer and possibly other cancers. Thus improving vitamin D status could be potentially beneficial against either incidence or mortality, or both."*

-E Giovannucci (#218)

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*"In this case-control study of North Carolina women, we found only very limited support for the hypothesis that vitamin supplement use is associated with a decreased risk of breast cancer. Among white women, any use of multivitamins, vitamin C or vitamin E in the past five years was each associated with an approximately 20% decrease in breast cancer risk; however, the confidence intervals around these estimates all included one. There was no evidence of a dose-response relationship between duration of use and breast cancer risk. In contrast to the modest inverse associations with certain vitamin supplements suggested for white women, there was essentially no evidence of a protective effect among black women for any of the vitamins examined."*

- PG Moorman, et al. (#259)

*"In this cohort, we observed a statistically significant inverse association between vitamin E intake and bladder cancer risk, which was strongest among those who had been taking vitamin E supplements for many years. A suggestive inverse association was noted for intake of vitamin C supplement dose and bladder cancer risk. No associations were observed between intake of total energy, macronutrients, or other micronutrients and bladder cancer risk."*

-DS Michaud (#254)

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"In the 11 non-hormone-dependent cancer sites described above, 46 studies have specifically reported on a vitamin C index or plasma ascorbate values; 33 of these found statistically significant protective effects, and several more were in the protective direction but did not achieve significance. None has found elevated risk with increasing intake. In addition to those, 29 studies reported on the effect of fruit consumption, 21 of which found significant protection associated with frequent consumption or high risk associated with low consumption. For oral, esophageal, gastric, and pancreatic cancer, the evidence is extremely strong, with virtually all studies showing a significant protective effect."

- G Block (#189)

"The SU.VI.MAX trial followed a pragmatic approach in testing the effect of a combination of 5 antioxidant vitamins or mineral at low doses. It is thus not possible to identify which individual micronutrient or combination is responsible for the preventative effect observed. Nevertheless, our study results support the hypothesis that chemoprevention of prostate cancer can be achieved with antioxidant vitamins and minerals."

- F Meyer, et al. (#253)

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*"Our study of nearly 1100 incident cases of cancer is one of the largest prospective studies of serum selenium levels and cancer risk and has more site-specific cancers than any previous study. We found highly significant ( $p < 10^{-4}$ ) inverse associations of serum selenium levels with the incidence of both esophageal and gastric cardia cancers over a period of 5.25 years of follow-up. Individuals in the highest quartile of selenium developed these cancers at approximately half the rate as individuals in the lowest quartile."*

-SD Mark, et al. (#248)

*"Total vitamin B6 intake was also statistically significantly inversely associated with risk of colorectal cancer. We observed 59 cases of colorectal cancer among the 25% of women (approximately 8200) with the lowest plasma vitamin B6 concentrations over the 10-year follow-up, compared with 33 cases of colorectal cancer in the 25% of women with the highest plasma vitamin B6 concentrations."*

-EK Wei, et al. (#288)

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"Based on overall consideration of results from observational and laboratory studies, the existing evidence is consistent with the hypothesis that increasing vitamin D3 intake to 1000-2000 IU per day or raising the serum level of 25(OH)D to 33 ng/mL or higher would be associated with substantially lower incidence rates of colorectal cancer, with only minimal risks."

-ED Gorham, et al. (#222)

"So far, epidemiological data for cancer argue for an overall positive role of sun-induced vitamin D. There may be more beneficial than adverse effects of moderately increased sun exposure, even for total cancer mortality. This message should be addressed to populations at risk for vitamin D deficiency."

- J Moan, et al. (#255)

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"Optimizing micronutrient intake (through better diets, fortification of foods, or multivitamin-mineral pills) can have a major impact on public health at low cost. Other micronutrients are likely to be added to the list of those whose deficiency causes DNA damage in the coming years. Tuning-up human metabolism, which varies with genetic constitution and changes with age, is likely to be a major way to minimize DNA damage, improve health and prolong healthy lifespan."

- BN Ames (#184)

"In conclusion, our findings do not support a protective role of calcium and vitamin D intakes against colorectal cancer incidence. However, given the strong evidence from both animal studies and in vitro studies, the benefits of these two nutrients cannot be ruled out. More detailed investigation of the interaction of calcium with other nutrients, including vitamin D, and additional questions better characterizing vitamin D status may be necessary to elucidate the true associations of calcium and vitamin D with risk of colorectal cancer."

-J Lin, et al. (#246)

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*"In our study, vitamin E showed no overall effect on lung cancer; however, preliminary analyses indicate possible efficacy with longer duration of intervention. Prostate cancer incidence was 34% lower in the vitamin E group and colorectal cancer was 16% lower, the latter being consistent with recent observational data suggesting such a protective association. Such effects, if corroborated by other studies, would have substantial public health consequences on two common malignancies."*

- D Albanes, et al. (#182)

*"On a very simplistic level, cancer is thought to arise because of an excess of DNA damage and/or the inappropriate expression of critical genes. Folate has consequently been of particular interest as a potential cancer protective agent because of the important roles it plays in nucleotide synthesis, as well as in the biological methylation of molecules such as DNA, RNA, proteins, and the phospholipids."*

- SW Choi, et al. (#199)

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*"In summary, overall risks for prostate cancer were unaffected by supplemental dietary antioxidant use among participants in the PLCO Trial; however, vitamin E supplementation in smokers and  $\beta$ -carotene supplementation in men with low dietary  $\beta$ -carotene were associated with reduced risks of this disease."*

-VA Kirsh, et al. (#234)

*"Our study, performed in individuals not selected for risk factors, indicates that a 7.5-year low-dose antioxidant supplementation lowered total cancer incidence in men but not in women. A similar tendency was observed for all-cause mortality."*

-S Hercberg (#228)

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## Bone and Joint Health

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*"[Boron] may have a preventive or therapeutic effect that helps to diminish bone mineral loss in susceptible populations."*

- SL Meacham, et al. (#355)

*"One member in each twin pair was randomly assigned using computer-generated numbers to receive 800 mg of elemental Calcium from citrate and carbonate, 400 IU of vitamin D<sub>3</sub> (as Cholecalciferol), 400 mg of Magnesium from citrate, and amino acid chelate and oxide in four orange-flavoured chewable tablets (Active Calcium™ Chewable); the other twin was given a matched placebo in a double-blinded manner. The placebo tablet was identical in appearance, taste and composition but contained no active ingredient. All tablets were supplied by USANA Health Sciences, Inc., Sydney, Australia..."*

- DA Greene, et al. (#331)

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*"In summary, dietary supplementation with a combination of nutritionally relevant amounts of vitamin K with vitamin D and calcium in healthy older women was associated with a modest but significant increase in BMC at one site, consisting predominantly of trabecular bone. Similar changes were not observed in either the vitamin K group alone or in the calcium plus vitamin D group, suggesting a synergistic role of the combination as suggested by previous reports."*

- C Bolton-Smith, et al. (#303)

*"Our particular contribution has been to extend from animal models to humans the essentiality of Cu, Mn and Zn in the development and maintenance of BMD [bone mineral density]... Through understanding the value of trace elements from food or supplements, and through sensible dietary strategies, we can slow the rate of bone loss, thus delaying or preventing osteoporosis, in a simple and inexpensive manner."*

- PD Saltman, et al. (#375)

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"Much evidence indicates that both calcium and vitamin D are efficacious in protecting the skeleton, particularly when these 2 nutrients are used in combination. Each nutrient is necessary for the full expression of the effect of the other, and where their actions are independent, their effects on skeletal health are complementary. Nutrient status for both tends to be deficient in the adult population of the industrialized nations. Hence, supplementation or food fortification with both nutrients is appropriate and, given contemporary diets and sun exposure, probably necessary."

- RP Heaney (#338)

"Adequate nutrition plays a major role in the prevention and treatment of osteoporosis; the nutrients of greatest importance are calcium and vitamin D. Numerous studies have shown that higher calcium intake at various ages are associated with higher bone mineral density compared with the bone mass of those with lower calcium intakes. In older postmenopausal women, the benefits of vitamin D and calcium supplementation in preventing bone loss, decreasing bone turnover, and decreasing non-vertebral fractures are clear."

- JW Nieves (#362)

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- J Adams, et al. (#295)

*"Osteoporosis is a multifactorial disorder, and, despite the considerable influence of heredity, bone health depends on the whole range of other nutrients and foods as well as the environmental factors. The prolonged deficiency or excess of one or the combination of several, as well as the changes in requirements of those nutrients caused by physiological and metabolic changes, might contribute to osteoporosis."*

- JZ Ilich, et al. (#342)

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*"In the presence of osteoporosis, vitamin D insufficiency may amplify bone loss and thus enhance fracture risk. It follows that at any age, but particularly in the elderly, an adequate intake of both calcium and vitamin D is important for the preservation of bone mass and prevention of osteoporosis."*

- C Gennari (#328)

*"The effects of low intakes of minerals important to normal bone metabolism need further investigation. An inadequate intake or imbalance of one or several of the minerals critical to bone development may jeopardize normal bone metabolism. There has been widespread interest over the years in assuring adequate calcium intakes at critical stages of the female life cycle. This interest should be extended to emphasize optimal intakes of all minerals known or suspected to affect bone mineral density, such as calcium, phosphorus, magnesium, and boron."*

- SL Meacham, et al. (#356)

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*"Collectively, our data provide evidence supporting dietary supplementation of n-3 PUFA [omega-3 polyunsaturated fatty acids], which in turn may have a beneficial effect of slowing and reducing inflammation in the pathogenesis of degenerative joint diseases in man."*

- CL Curtis, et al. (#317)

*"In summary, spinal bone loss in a small group of older postmenopausal women was slowed by supplementation with calcium as CCM [calcium citrate malate] and was halted by supplementation with a mineral cocktail composed of CCM along with zinc, manganese and copper. Only the group supplemented with calcium plus trace minerals differed from the placebo group, which, as expected, lost a significant amount of bone density."*

- L Strause, et al. (#381)

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- CS Yajnik, et al. (#495)

*"In conclusion, relatively modest amounts of dietary docosahexaenoic acid during pregnancy appear to extend gestational age and may lead to enhanced fetal growth."*

- CM Smuts, et al. (#480)

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"Dosing recommendations for mothers during pregnancy should be aimed at preventing problems in neonates and infants, and a vitamin D dose sufficient for the mother during pregnancy should produce normal cord blood 25(OH)D concentrations at birth. Giving relatively small doses of vitamin D directly to the infant or supplementing the mother with 100 µg (4000 IU) vitamin D daily should maintain normal 25(OH)D concentrations in exclusively breastfed infants without harming the mother."

- CS Kovacs (#452)

"Given the results of this study, we think that all women planning pregnancy should receive a vitamin supplement containing folic acid."

- AE Czeizel, et al. (#417)

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*"The recommendations for dietary omega-3 fatty acids should be adopted at the onset of pregnancy, but there may be benefits for all women who are considering becoming pregnant. Given concerns for mercury toxicity with overconsumption of certain fish, in order to meet these recommendations, pregnant women will need to consume omega-3 fatty acids from 3 sources: vegetable oils, 2 servings of seafood per week, and omega-3 fatty acid supplements containing EPA and DHA or DHA alone."*

- JA Greenberg, et al. (#430)

*"Our study demonstrates an association between maternal vitamin B12 status during pregnancy and children's cognitive functioning. Higher maternal plasma vitamin B12 concentration in pregnancy was an independent predictor of the child's cognitive performance on the CTT-A and Digit Span Backward tests, after controlling for a number of possible confounders, including the child's own vitamin B12 status at 6 years of age."*

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"Omega-3 fatty acid (dietary or in capsules) ensures that a woman's adipose tissue contains a reserve of these fatty acids for the developing fetus and the breast-fed newborn infant. This ensures the optimal cerebral and cognitive development of the infant. The presence of large quantities of EPA and DHA in the diet slightly lengthens pregnancy, and improves its quality."

- JM Bourre (#405)

"This trial demonstrates that the visual maturation of healthy infants is improved by continued supplies of DHA from both human milk and DHA-enriched baby foods well into 1 y of life."

- DR Hoffman, et al. (#439)

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*"In summary, our data strongly suggest that zinc supplementation improves pregnancy outcome in at least some pregnant women, and we support the inclusion of zinc in prenatal multivitamin/mineral tablets."*

*- RL Goldenberg, et al. (#428)*

*"This study indicates that maternal supplementation with very-long-chain n-3 PUFAs during pregnancy and lactation improves the intelligence of children at 4 years of age."*

*- IB Helland, et al. (#435)*

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- G Hornstra (#443)

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- R Uauy, et al. (#485)

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# Immune Function

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"The common denominator that rises from these studies is that vitamin D affects the immune system at many levels and by a number of mechanisms. It takes part in the genetic regulation of cytokine production, VDR expression and affects important biological processes by which these cells interact."

- Y Arnson, et al. (#506)

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*"The elucidation of the precise roles of vitamin D in the immune system and in the pathogenesis of multiple diseases has the potential to have profound effects on our ability to prevent and treat these disorders."*

- NE Lange, et al. (#563)

*"Inadequate intake and status of vitamins and trace elements may lead to suppressed immunity, which predisposes to infections and aggravates undernutrition. Evidence has accumulated that in humans certain nutrients selectively influence the immune response, induce dysregulation of a coordinated host response to infections in cases of deficiency and oversupply, and that deficiency may impact virulence of otherwise harmless pathogens. Thus, micronutrients are required at appropriate intakes for the immune system to function optimally. Available data indicate a role of vitamins (A, D, E, B6, B12, folate, and C), and trace elements (selenium, zinc, copper, and iron) on the immune response... Overall, inadequate intake and status of these vitamins and trace elements may lead to suppressed immunity, which predisposes to infections and aggravates malnutrition. Therefore, supplementation with these selected micronutrients can support the body's natural defence system by enhancing all three levels of immunity."*

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*"In summary, our results show that the age-associated defect in the redistribution of signaling molecules to the immunological synapse is reversed by vitamin E. This effect is strongest in naive T cells, which exhibit the age-related defects in protein recruitment and T cell activation. This is the first demonstration of a reversal of a key early signaling defect in aged T cells by a nutrient. These findings have important implications for the development of preventive and therapeutic strategies to reduce age-associated defects in T cells."*

- MG Marko, et al. (#569)

*"Because aging and malnutrition exert cumulative influences on immune responses, many elderly people have poor cell-mediated immune responses and are therefore at a high risk of infection. Nutritional therapy may improve immune responses of elderly patients with protein-energy malnutrition. Supplementation with high pharmacologic doses of a single nutrient (zinc or vitamin E) may be useful for improving immune responses of self-sufficient elderly people living at home. Therefore, nutritional deficiency must be treated in the elderly to reduce infectious risk and possibly slow the aging process."*

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"Investigators have demonstrated how appropriate serum concentrations of vitamin D facilitate the ability of immune cells to defend against bacterial and viral infections. Ongoing research in this area has provided new ways of understanding the immune system and how the pleiotropic actions of vitamin D serve an important immunoregulatory role in proper immune function. With the increasing evidence of vitamin D insufficiency's detrimental effects beyond the classically defined cause of rickets, the full story behind the role of vitamin D insufficiency/deficiency in pediatric infection and immune function awaits full elucidation."

- VP Walker, et al. (#602)

"Although our study suggests that many elderly individuals might benefit from a supplementary intake of vitamin E, such public health recommendations can only be considered after longer-term studies with lower amounts of tocopherol are completed. This point will be especially important in determining if the immunostimulatory effect observed is due to pharmacologic or physiologic effect of vitamin E. Nevertheless, it is encouraging to note that a single nutrient supplement can enhance immune responsiveness in healthy elderly subjects consuming the recommended amounts of all nutrients. This is especially significant because dietary intervention represents the most practical approach for delaying or reversing the rate of decline of immune function with age."

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*"In conclusion, our double-blind, placebo-controlled study shows that levels of vitamin E higher than currently recommended enhance in vivo indexes of T cell-mediated function in healthy elderly. The enhancement of cell-mediated immunity by vitamin E was not associated with any adverse effects. Since age-associated decline in immune response is associated with increased morbidity and mortality in the elderly and is widely observed, recommendations to increase the intake of vitamin E for elderly should be considered."*

- EG Pallast, et al. (#584)

*"In summary, the present study demonstrates that modest daily doses of micronutrients given for 1 y can enhance cellular immunity and can also prevent the development of biochemical evidence of micronutrient deficiencies in healthy, independently living older people. These results suggest that the dietary micronutrient intake of older people and/or the current RDAs for one or more micronutrients may be too low to support optimal immunity in older individuals."*

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*"Although many open questions remain, there is promise that vitamin A and D metabolites or their analogues have the potential to be used in clinical settings for therapeutic benefit. In particular, it will be important to assess the impact of using 1,25(OH)<sub>2</sub>VD<sub>3</sub> analogues as an adjuvant immunomodulatory therapy in the setting of autoimmune diseases and in transplant recipients. It will also be important to determine the net effects of retinoic acid or synthetic RAR-agonists, especially in the intestine, where these agents appear to have a role in enhancing immune responses. The capacity of vitamin A metabolites to foster gut-homing T cells might improve strategies of mucosal vaccination or aid in decreasing pathogenic immunity by potentiating the induction of T<sub>Reg</sub> cells."*

- JR Mora, et al. (#574)

*"Nutritional intervention has proven to be a practical approach in modulating dysregulated immune and inflammatory responses. The efficacy of such intervention, as with vitamin E, for example, has been demonstrated in clinical trials using infections as an endpoint. At the same time, mechanistic studies have deciphered how vitamin E affects T cell functions at cellular and molecular levels and thus, lend further support to the efficacy of nutrient supplementation in modulating the age-related immune dysregulation."*

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- F Girodon, et al. (#544)

"The results of this study substantiate the hypothesis that nutritional status is an important determinant of immunocompetence in old age and that an optimum intake of micronutrients is needed for enhanced immune responses in elderly subjects. Such an intervention led to a striking reduction in illness, a finding that is of considerable clinical and public-health importance."

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## Healthy Vision

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*"We found that high dietary intake of vitamin E and zinc was associated with a lower risk of incident AMD [age-related macular degeneration]. An above-median intake of the combination of vitamins C and E, beta carotene, and zinc was associated with a 35% lower risk of incident AMD."*

- R van Leeuwen, et al. (#677)

*"A daily dose of 10 mg lutein supplementation induced an increase in mean plasma lutein by a factor of 5 and a linear 4-week increase in relative MP [macular pigment] density of 4% to 5%. To our knowledge, this is the first study in which the effects of intake of lutein have been assessed with objective measurement techniques. In particular, the SLO-based technique provided very reliable results. With this technique all subjects showed a significant increase in MP density."*

- TTJM Berendschot, et al. (#616)

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-PR Trumbo, et al. (#676)

"In this large prospective study, we observed a modest inverse association between intake of lutein and zeaxanthin and extraction of cataracts. Men in the highest fifth of lutein and zeaxanthin intake had a 19% lower risk of cataract extraction compared with those in the lowest fifth of intake. There was no significant association between intake of vitamin A or other carotenoids and risk of cataract in multivariate analyses. Increased consumption of some foods high in lutein, including broccoli and spinach, was associated with a lower risk of cataract extraction. The finding that increased intake of other fruit and vegetables was not associated with a decreased risk suggests that the relation may be specifically due to lutein and zeaxanthin and not simply to a healthy lifestyle."

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-JM Seddon (#668)

*"The results of our LAST [Lutein Antioxidant Supplementation Trial] study support the results of our pilot spinach data that lutein may be useful in the nutritional intervention of atrophic ARMD [age-related macular degeneration] in mid-western male subjects. In LAST, lutein enhanced macular pigment and visual function with AREDS stages II, III, and IV. Thus lutein supplementation may be beneficial at all stages of ARMD. Further studies with more patients of both genders are needed to determine the long-term effect of lutein alone or lutein together with a broad spectrum of antioxidants, vitamins, and minerals on patients with atrophic age-related macular degeneration."*

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*"In summary, the results of the present study provide added support for a relation between nutrient intake and nuclear opacification. Our observation that vitamin E intake is associated with a reduction in nuclear opacification is consistent with other longitudinal studies, strengthening the hypothesized role for this specific nutrient in nuclear cataract formation, and the associations with riboflavin, thiamin, and niacin should serve to focus added effort on examining the role of these nutrients in the development of nuclear cataract."*

- PF Jacques, et al. (#639)

*"In this large prospective study, those with the highest intake of lutein and zeaxanthin had a 22% lower risk of cataract extraction than did those in the lowest quintile of intake (RR: 0.78; 95% CI:0.63, 0.95; P for trend = 0.04) after age, smoking, and other potential cataract risk factors were controlled for. Other specific carotenoids (α-carotene, β-carotene, lycopene, and β-cryptoxanthin), vitamin A, and retinol were not associated with cataract in multivariate analysis. Increasing frequency of intake of spinach and kale, foods rich in lutein, was associated with a moderate decrease in risk. The observation that other fruit and vegetables were not associated with decreased risk suggests that the relation may be due to lutein, a specific carotenoid predominantly found in spinach and kale, and not to a healthy lifestyle per se."*

- L Chasan-Taber, et al. (#625)

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- A Taylor, et al. (#673)



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