# Vitamins for Chronic Disease Prevention in Adults

## Clinical Applications

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**Vitamin deficiency syndromes such as scurvy and beriberi are uncommon in Western societies. However, suboptimal intake of some vitamins, above levels causing classic vitamin deficiency, is a risk factor for chronic diseases and common in the general population, especially the elderly. Suboptimal folic acid levels, along with suboptimal levels of vitamins $B_6$ and $B_{12}$, are a risk factor for cardiovascular disease, neural tube defects, and colon and breast cancer; low levels of vitamin D contribute to osteopenia and fractures; and low levels of the antioxidant vitamins (vitamins A, E, and C) may increase risk for several chronic diseases. Most people do not consume an optimal amount of all vitamins by diet alone. Pending strong evidence of effectiveness from randomized trials, it appears prudent for all adults to take vitamin supplements. The evidence base for tailoring the contents of multivitamins to specific characteristics of patients such as age, sex, and physical activity and for testing vitamin levels to guide specific supplementation practices is limited. Physicians should make specific efforts to learn about their patients' use of vitamins to ensure that they are taking vitamins they should, such as folate supplementation for women in the childbearing years, and avoiding dangerous practices such as high doses of vitamin A during pregnancy or massive doses of fat-soluble vitamins at any age.**

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IN THE ABSENCE OF SPECIFIC PREDISposing conditions, a usual North American diet is sufficient to prevent overt vitamin deficiency diseases such as scurvy, pellagra, and beriberi. However, insufficient vitamin intake is apparently a cause of chronic diseases. Recent evidence has shown that suboptimal levels of vitamins, even well above those causing deficiency syndromes, are risk factors for chronic diseases such as cardiovascular disease, cancer, and osteoporosis. A large proportion of the general population is apparently at increased risk for this reason.

### Suboptimal Amounts of Vitamins

Suboptimal levels of a vitamin can be defined as those associated with abnormalities of metabolism that can be corrected by supplementation with that vitamin. For example, many people in the general population have serum homocysteine levels from 1.62 to 2.03 mg/L (12-15 µmol/L),[1] which fall to baseline levels of 1.08 to 1.35 mg/L (8-10 µmol/L) after a few weeks of supplementation with folate, along with vitamins $B_{12}$ and $B_6$.[2] Similarly, in many elderly people, methylmalonic acid levels fall with vitamin $B_{12}$ supplementation,[2] and elevated levels of parathyroid hormone fall with vitamin D supplementation.[3] Measurements of vitamin levels in blood, serum, or red blood cells, at least with current reference points for abnormality, are not a reliable guide to this form of deficiency; in one study,[2] supplementation substantially reduced serum homocysteine levels in elderly patients with normal serum folate concentrations.

For some vitamins, the concept of suboptimal levels is also supported by randomized trial evidence that supplementation reduces the rate of clinical

**See also p 3116 and Patient Page.**

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events. The research evidence is conclusive that folate during the first trimester of pregnancy reduces the risk of neural tube defects in women at increased risk.[4] Similarly, vitamin D supplementation, along with calcium, reduces the risk of fractures in elderly women with osteoporosis.[5]

The high prevalence of suboptimal vitamin levels implies that the usual US diet provides an insufficient amount of these vitamins. Fruits and vegetables are the main dietary source of many vitamins, and health experts have long recommended at least 5 daily servings. A recent survey showed that only 20% to 30% of the population actually meet this goal.[6] Although vitamin D is added to milk, many people (especially the elderly) do not consume enough dairy products to get a sufficient amount of vitamin D.[3,7,8] Folate supplementation of cereal products is sufficient to raise folate intake only by about 100 µg, so many people do not meet the goal of 400 µg/d.[9] Food preparation may decrease the activity for some vitamins; for example, keeping food hot longer than 2 hours results in a more than 10% loss of vitamin C, folate, and vitamin $B_6$.[10] Vitamins are also lost during chilling, storage, and reheating, including more than 30% of vitamin C and folate.[10] Alcohol consumption increases folate requirements,[11] and aging is associated with decreased absorption of some vitamins such as $B_{12}$.

## Correcting Suboptimal Vitamin Levels

Three options exist for correcting suboptimal vitamin intake. First, physicians could counsel patients to improve their diet. This approach would be relatively inefficient if the only goal were to increase vitamin consumption because patients would have to be counseled individually, and it is difficult to get individual patients to change their diets. Nevertheless, dietary change is a central component of an overall program of preventive care.[12] Foods contain thousands of compounds that may be biologically active, including hundreds of natural antioxidants, carotenoids, and flavonoids. For these reasons, vitamin supplementation is not an adequate substitute for a good diet.

A second option is to add vitamins to generally consumed foods. The United States has been adding vitamin D to milk and some other dairy products since the 1930s because of the high prevalence of rickets and osteomalacia in northern climates at that time. Beginning in 1996, folate has been added to cereals to reduce the rate of neural tube defects. However, this approach is limited by popular mistrust of adding chemicals to food.

A third option is for individuals to take vitamin supplements. All major pharmacies carry their own brands of multivitamins as well as a variety of other brand name and generic multivitamins. The contents of basic multivitamins are remarkably similar across brands, with each having at least 100% of the daily value for nearly all vitamins (with the exception of vitamin K). In addition to vitamins, so-called multivitamins often contain other food supplements such as minerals and herbs. The amount of calcium in multivitamins is typically between 40 and 160 mg, well below the generally recommended dose of 1000 to 1500 mg/d,[13] so one cannot depend on multivitamins for meeting calcium needs. Most multivitamins contain iron, whose supplementation may not be advisable for men and nonmenstruating women, given the high prevalence of the gene for hemochromatosis.

The cost for brand-name multivitamins may be around $20 to $30 annually, and some special formulations may cost a great deal more. However, one can easily buy large quantities (eg, 250-500 pills) of generic multivitamins for around $10 annually. We are aware of no evidence that the various multivitamins differ in bioavailability because of the way they are formulated. Patients can buy individual vitamins at an even lower price, which may make sense for women in the childbearing years, for whom folate supplementation might cost only $5 to $10 annually.

Special multivitamins are sold for subgroups of the population such as active men, perimenopausal women, and the elderly. The Internet and health-food stores are filled with promotions for these special-purpose multivitamins, which are often costly. The only evidence-based arguments for taking more than a common multivitamin once a day pertain to the elderly and women who might become pregnant. The recommended intake for vitamins $B_{12}$ and D in the elderly is closer to 2 times the dietary reference intake. For women who might become pregnant, folate at 800 µg/d is appropriate.

Some vitamins, such as thiamin, riboflavin, and niacin, have received little mention in this review. Although by definition severe deficiency of these vitamins is associated with disease, they have so far not been associated with chronic diseases. The absence of evidence that these vitamins are associated with chronic diseases might be because those associations do not exist, ordinary diets provide sufficient amounts to prevent chronic disease, or the research has not yet been done to discover these relationships.

## Testing

Tests for vitamin levels in blood, serum, or red blood cells are now offered by commercial laboratories, as are tests for substances such as homocysteine that mark abnormal vitamin-related metabolism.[14] The availability of these tests raises these questions: Would this additional information lead to better preventive or therapeutic interventions than might be offered without the test? If so, what kind of patients would benefit?

It is certainly possible that some individuals, because of their diets or genetic polymorphisms, have unusual vitamin needs. Many of these people can be detected by a simple review of their medical problems, including alcoholism. The *MTHFR* polymorphism, which is associated with low folate levels and perhaps increased rates of cardiovascular disease, is the best studied. The abnormal *MTHFR* gene occurs in 5% to 15% of the population[15] and might have effects on diseases related to folate deficiency. The *MTHFR* gene would be detected only by specific testing not yet

 

commercially available. However, research into the metabolic and clinical effects of these disorders is in its infancy and not strong enough to confidently guide tailored supplementation programs. Therefore, we believe that testing individuals who do not have a well-recognized indication is premature.

## Recommendations

We recommend that all adults take one multivitamin daily. This practice is justified mainly by the known and suspected benefits of supplemental folate and vitamins $B_{12}$, $B_6$, and D in preventing cardiovascular disease, cancer, and osteoporosis and because multivitamins at that dose are safe and inexpensive.[16] It is reasonable to consider a dose of 2 ordinary multivitamins daily in the elderly, specifically because of the high prevalence of suboptimal vitamin $B_{12}$ and D intake. However, it might be safer to supplement 1 multivitamin with additional vitamins $B_{12}$ and D, taken separately, given the possibility that increased vitamin A intake might increase the risk of hip fracture[17] and that the iron in most multivitamins may increase the risk of hemochromatosis in some people. The increased folate requirement in people with high alcohol intake can be met with 1 multivitamin daily or folic acid supplementation alone. For women attempting to conceive, a multivitamin plus folate at 400 µg/d is appropriate, given evidence of additional benefit with higher folate levels.[18] 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.

Physicians often do not ask about vitamin use. Patients may not volunteer information about their vitamin use, fearing that the physician would disapprove of unconventional use of vitamins. Therefore, physicians should specifically ask about vitamin use with 2 goals in mind. First, they should be sure that patients know about the vitamin supplements they clearly should be taking, such as folate during the childbearing years. Second, physicians should be sure the patient is not taking vitamins in harmful doses, such as very large doses of vitamin D or even moderate doses of vitamin A during the first trimester of pregnancy. Within these rather broad limits, we believe that physicians should be interested and not directive, even when it seems the patient has unfounded beliefs or apparently unhelpful practices. In this way, physicians can avoid incurring a substantial chance of losing access to important information about patients' vitamin use.

## Additional Information About Vitamins

The evidence base for the clinical effects of vitamins is increasing rapidly. For physicians to keep up with new developments, there is no good alternative to electronic sources. The World Wide Web includes a vast array of information on vitamins, most of it promotional and self-serving. Physicians can find the most updated and credible information at the National Institutes of Health Web site (http://www.cc.nih.gov/ccc/supplements). In addition, Tufts University maintains an excellent nutrition Web site, as well as a Nutrition Navigator that provides quality ratings for other nutrition Web sites (http://www.navigator.tufts.edu). This site includes appropriate information for patients and health care professionals. Some textbooks and Web publications are continually updated as new research findings are published. The Institute of Medicine has published a series of books on this subject as well, with extensive review of the existing literature at the date of publication.[19-23]

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### REFERENCES

**1.** Ward M, McNulty H, McPartlin J, Strain JJ, Weir DG, Scott JM. Plasma homocysteine, a risk factor for cardiovascular disease, is lowered by physiological doses of folic acid. *QJM*. 1997;90:519-524.
**2.** Naurath HJ, Joosten E, Riezler R, Stabler SP, Allen RH, Lindenbaum J. Effects of vitamin B12, folate, and vitamin B6 supplements in elderly people with normal serum vitamin concentrations. *Lancet*. 1995;346:85-89.
**3.** Gloth FM III, Gundberg CM, Hollis BW, Haddad JG Jr, Tobin JD. Vitamin D deficiency in homebound elderly persons. *JAMA*. 1995;274:1683-1686.
**4.** MRC Vitamin Study Research Group. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. *Lancet*. 1991;338:131-137.
**5.** Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997;337:670-676.
**6.** Flood A, Schatzkin A. Colorectal cancer: does it matter if you eat your fruits and vegetables? *J Natl Cancer Inst*. 2000;92:1706-1707.
**7.** Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. *N Engl J Med*. 1998;338:777-783.
**8.** Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly. *Endocr Rev*. 2001;22:477-501.
**9.** Jacques PF, Selhub J, Bostom AG, Wilson PW, Rosenberg IH. The effect of folic acid fortification on plasma folate and total homocysteine concentrations. *N Engl J Med*. 1999;340:1449-1454.
**10.** Williams PG. Vitamin retention in cook/chill and cook/hot-hold hospital food-services. *J Am Diet Assoc*. 1996;96:490-498.
**11.** Hillman RS, Steinberg SE. The effects of alcohol on folate metabolism. *Annu Rev Med*. 1982;33:345-354.
**12.** Office of Disease Prevention and Health Promotion. Healthy people [US Dept of Health and Human Services Web site]. Available at: http://www.health.gov/healthypeople. Accessibility verified April 8, 2002.
**13.** National Institutes of Health Consensus Conference. Optimal calcium intake: NIH Consensus Development Panel on Optimal Calcium Intake. *JAMA*. 1994;272:1942-1948.
**14.** Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency. *Arch Intern Med*. 1999;159:1289-1298.
**15.** Molloy AM, Daly S, Mills JL, et al. Thermolabile variant of 5,10-methylenetetrahydrofolate reductase associated with low red-cell folates. *Lancet*. 1997;349:1591-1593.
**16.** Oakley GP Jr. Eat right and take a multivitamin. *N Engl J Med*. 1998;338:1060-1061.
**17.** Feskanich D, Singh V, Willett WC, Colditz GA. Vitamin A intake and hip fractures among postmenopausal women. *JAMA*. 2002;287:47-54.
**18.** Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. *Lancet*. 2001;358:2069-2073.
**19.** Committee on Diet and Health NRC. *Diet and Health: Implications for Reducing Chronic Disease Risk*. Washington, DC: National Academy Press; 1989.
**20.** Institute of Medicine. *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*. Washington, DC: National Academy Press; 2000.
**21.** Institute of Medicine. *Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids*. Washington, DC: National Academy Press; 2000.
**22.** Institute of Medicine. *Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc*. Washington, DC: National Academy Press; 2001.
**23.** Institute of Medicine. *Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride*. Washington, DC: National Academy Press; 1999.