INTRODUCTION — Vitamins are chemically unrelated organic compounds, or families of organic compounds, that are essential in small amounts for normal metabolism. Because vitamins (with the exception of vitamin D) cannot be synthesized by humans, they need to be ingested in the diet to prevent disorders of metabolism. They should be distinguished from minerals (such as calcium and iron), some of which are also essential micronutrients. "Food supplements" is a general term for vitamins, minerals, herbs, and other natural compounds claimed to improve health when taken in small amounts as alternatives or supplements to drugs. (See "Overview of dietary trace minerals" and "Overview of herbal medicine and dietary supplements".)

When vitamin deficiency is defined as low blood levels, or levels associated with reversible metabolic changes, the prevalence on usual Western diets is higher than generally believed, especially in the elderly. Pregnancy and alcohol consumption may increase requirements for some vitamins. Subtle deficiencies in several vitamins, at levels below that causing classic vitamin deficiency syndromes (eg, scurvy or pellagra) have been associated in observational studies with chronic degenerative diseases such as atherosclerosis, cancer, and osteoporosis. However, it is less well established that the vitamins in supplements can prevent or reverse chronic diseases.

The evidence for using vitamin supplementation to prevent chronic disease is reviewed here. Overviews of individual vitamins, including deficiency syndromes and vitamin toxicity, appear separately. (See "Overview water-soluble vitamins" and "Overview of vitamin A" and "Overview of vitamin D" and "Overview of vitamin E").

VITAMIN DEFICIENCY — The concept of vitamin deficiency has evolved since vitamins were first discovered, from obvious vitamin deficiency syndromes to the subtle effects of suboptimal vitamin intake on chronic diseases.

Gross vitamin deficiency may be recognized by obvious clinical syndromes (table 1). These syndromes are seen in areas of the world with very poor diets; in Western societies they occur mainly in special populations, including the elderly, vegans, new immigrants, the very poor, patients with alcoholism, malabsorption, little sun exposure, history of gastric bypass surgery, and inborn errors of metabolism, and those undergoing hemodialysis or receiving parenteral nutrition (table 2).

Dietary reference intakes (DRIs) represent four concepts: the Recommended Daily Allowance (RDA); Adequate Intake (AI); Estimated Average Requirement (EAR); and Tolerable Upper Level (UL). DRIs are established in the United States by the National Academy of Sciences, National Research Council, and the Institute of Medicine. For clinical purposes, we still refer to the RDA, which is the average daily intake that is sufficient to meet the dietary requirement of nearly all healthy people. The AI is used when the RDA cannot be determined (as is still the case for vitamins D and K) (table 3). However, these levels may not be adequate for preventing chronic disease in some people.

Measurement of serum levels of several vitamins are commercially available. They are useful if clearly very high or very low to diagnose or rule out gross deficiency. However, the meaning of a "normal" value is uncertain; it is defined as the range of usual values in the general population, but many of these people may have suboptimal intake (just as, for example, commonly occurring levels of cholesterol or blood pressure may be harmful).

Intake or serum levels of some vitamins have been related to biochemical abnormalities. As examples, the serum concentration of homocysteine rises with diets low in folic acid, methylmalonic acid rises with low intake of vitamin B12, and parathyroid hormone rises with low intake of vitamin D. These biochemical abnormalities generally improve with increasing intake and reach a plateau beyond which more intake causes no further reduction, suggesting a correctable metabolic disorder.
Vitamins are chemically unrelated organic compounds, or families of organic compounds, that are "Overview of dietary trace ...". These syndromes are still defined as the range of usual values in the general population, but many of these people may have suboptimal intake.
Current interest in vitamins centers on whether optimizing the daily ingestion of vitamins can prevent chronic disease (eg, vitamin D supplementation and osteoporotic fractures; vitamin B12 and dementia). The remainder of this topic review will address the effectiveness of individual vitamins in preventing specific diseases.

**FOLIC ACID** — Folate is present in green, leafy vegetables, fruits, cereals and grains, nuts, and meats. Folic acid supplementation reduces the risk of neural tube defects, probably because folic acid is required for normal cell division. (See "Folic acid for prevention of neural tube defects") This has been shown in multiple observational studies and confirmed by a randomized, double-blind trial of 1817 women at high risk of having a fetus with a neural tube defect because of a previous affected pregnancy. The women were allocated at random to one of four groups: folic acid (4 mg/day); other vitamins; both; or neither. Of 1195 women with a completed pregnancy, 27 had a child with a neural tube defect: 6 in the two folic acid groups and 21 in the other two groups (a 72 percent reduction in the risk of this birth defect). The other vitamins showed no significant protective effect. Folic acid supplements may also reduce the risk of congenital anomalies other than neural tube defects, but this potential benefit has not been established by well-designed trials.

In a report of women from two areas of China, one with a high and one with a low rate of neural tube defects, periconception intake of 400 mcg of folic acid per day significantly reduced the incidence of neural tube defects in both regions. In the high incidence region, the rate of neural tube defects was 1.0 per 1000 among the fetuses or infants of women who were asked to take a pill containing 400 mcg of folic acid daily from the time of their premarital examination until the end of the first trimester of pregnancy, compared with 4.8 per 1000 among the fetuses or infants of women who did not take any folic acid. Comparable numbers for treated and untreated women in the low incidence region were 0.6 and 1.0 per 1000, respectively.

Although daily supplements containing 400 mcg of folic acid do decrease the rate of neural tube defects, larger doses appear to have greater protective effects. In one model, 400 mcg per day would reduce neural tube defects by 57 percent and 5000 mcg per day by 85 percent. The neural tube is formed between postconception days 15 to 28. Thus, folic acid must be taken at the time required for normal cell division. (See "Overview of homocysteine", section "Thermolabile variant of MTHFR").

Folic acid supplementation is important not only in the early stages of pregnancy, but throughout pregnancy. Folic acid needs increase during pregnancy, and supplementation (along with iron supplementation) helps prevent maternal anemia.

**Cardiovascular disease**— High levels of homocysteine are associated with an increased risk of cardiovascular disease. Supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels. However, randomized, controlled trials of supplementation for secondary prevention do not support the hypothesis that these vitamins are beneficial for cardiovascular disease. (See "Overview of homocysteine").

**Cancer**— Biological evidence suggests that sufficient folate intake might prevent cancers in certain populations at
Folic acid, the form of the vitamin included in supplements, has the same biologic effects as folate, but is more bioavailable and metabolism, occurring in 5 to 15 percent of the population, causes unusually. However, this abnormality does not appear "Overview of homocysteine," section.

This has been shown in . The women were allocated at completed pregnancy, 27 had a child with a neural tube defect: 6 in the two folic acid groups and 21 in the two other per day significantly reduced the incidence of neural tube defects in . In the high incidence region, the rate of neural tube defects was 1.0 per 1000 among the fetuses or infants of women who did not take any folic acid. Comparable numbers for treated and untreated women in do decrease the rate of neural tube defects, larger must be taken at the time (FDA) mandated in 1998 that cereal grain products be fortified with folic acid. The concentration of folic acid added, fortification in various regions of the world and at section.
Folate plays a key role in methionine regeneration. As a result, folate deficiency may contribute to aberrant DNA synthesis and carcinogenesis by decreasing methionine availability and interfering with normal DNA methylation. A functional polymorphism in methylenetetrahydrofolate reductase (MTHFR, a major enzyme involved in folate metabolism) is linked to colorectal cancer (figure 1). Folate might therefore protect DNA against damage during cell division (17). (See "Physiology of vitamin B12 and folic acid deficiency").

Observational studies have found associations between higher dietary folate intake and a reduced risk of colon cancer or colorectal adenoma, particularly in people who drink alcohol (15,18,19). While observational studies have not consistently found an association between folate intake and breast cancer (20), some studies have suggested that high folate intake decreases the risk of breast cancer in women with moderate or high alcohol consumption (21). (See "Overview of the risks and benefits of alcohol consumption", section on 'Colorectal').

In contrast to the biologic and observational evidence, randomized trials have not confirmed these benefits of folic acid supplementation and some have even raised the possibility of harm:

- A randomized trial of supplementation with folic acid (1 mg daily) or placebo in 1021 adults with a recent colorectal adenoma found no difference in the risk of a new adenoma on surveillance colonoscopy at three year (RR 1.04, 95% CI 0.90-1.20) (22). Risk of advanced lesions (tubulovillous adenomas, villous adenomas, leukoplakia, adenomas, adenomas with high grade dysplasia, or invasive cancer) was slightly elevated at three years, but not beyond chance (RR 1.32, CI 0.90-1.92).

  Among the 607 patients who underwent a second colonoscopy after six to eight years (three to five years after the initial surveillance colonoscopy), there was again no difference in new adenomas with folic acid (RR 1.13, CI 0.93-1.37), but the risk of advanced lesions was elevated (11.6 versus 6.9 percent, RR 1.67, CI 1.00-2.80).

  In addition, an analysis of adverse events found an increased rate of noncolorectal cancer in patients receiving folic acid (10.5 versus 6.3 percent) that appeared to be mainly attributable to an increase in prostate cancer (7.3 versus 2.8 percent).

- Another randomized trial of folic acid supplementation (0.5 mg daily) in patients with a colorectal adenoma found no effect on the risk of recurrent adenoma (RR 1.07, 95% CI 0.85-1.34) or advanced adenoma (RR 0.98 CI 0.68-1.40) (23). The difference in results between these previous two trials may have been due to the higher dose of folate used in the first trial.

- Combined analysis of two similarly designed trials in patients with ischemic heart disease found an increased risk for cancer incidence (HR 1.21, 95% CI 1.03-1.41) and cancer mortality (HR 1.38, 1.07-1.79) in participants who received folic acid (0.8 mg daily) plus vitamin B12 (0.4 mg daily) supplementation for a three year period and were followed for a subsequent three years (24). Cancer incidence and mortality were associated with higher serum folic acid levels, but not vitamin B12 levels, suggesting that the adverse effects were mediated by folic acid only.

- In contrast, a trial in the United States in 5442 female health professionals at high risk for cardiovascular disease, with more than seven years of follow-up, found that a B vitamin supplement (2.5 mg folic acid, vitamin B6, 1 mg vitamin B12) had no effect on the risk of invasive cancer (HR 0.97, 95% CI 0.79-1.18) [25].

Although the evidence from randomized trials is not conclusive, we recommend not taking folic acid supplementation for the sole purpose of reducing cancer risk. Recommendations for folic acid supplementation in pregnancy have not changed. (See ‘Pregnancy’ above.)

**Hypertension** — High folate intake may reduce the risk of hypertension. In multivariate analyses from the large prospective Nurses' Health Study, compared with women who consumed less than 200 mcg folate per day, the risk of hypertension was reduced in young women who consumed more than 1000 mcg per day (relative risk [RR] 0.54) and to a lesser extent in older women (RR 0.82) (26).

**Hearing loss** — There is conflicting observational evidence about whether increased serum folate levels are associated with a decreased risk of age-related hearing loss (27,28).

A randomized trial that addressed this issue was performed in 728 men and women ages 50 to 70 with elevated homocysteine levels (29). The study was performed in the Netherlands at a time when food was not supplemented with folic acid. Subjects who received daily supplementation with 800 mcg of folic acid for three years had a slight slower decline in low frequency hearing than those receiving placebo. No such difference was seen for decline in hearing in the high frequencies.

Additional studies are needed before folate supplementation can be recommended for the purpose of preventing...
Folate might therefore protect DNA against... observational studies have suggested... some studies have suggested... colorectal adenoma found no difference in the risk of a new adenoma on surveillance colonoscopy at three years. Risk of advanced lesions (tubulovillous adenomas, villous adenomas, large... Among the 607 patients who underwent a second colonoscopy after six to eight years (three to five years after the initial surveillance colonoscopy), there was again no difference in new adenomas with folic acid (RR 1.13, CI... found no effect on the risk of recurrent adenoma (RR 1.07, 95% CI 0.85–1.34) or advanced adenoma (RR 0.98,... supplementation for a three... 0.54). The study was performed in the Netherlands at a time when food was not supplemented... Subjects who received daily supplementation with 800 mcg of folic acid for three years had a slightly
Other — Elevated homocysteine levels have been associated with other conditions such as osteoporosis and dementia. It is not known whether these associations are causal or whether lowering homocysteine levels would affect risk. However, supplementation with folate and vitamin B12 in high risk groups may reduce the risk of fractures. (See "Overview of the management of osteoporosis in postmenopausal women", section on "Folate/vitamin B12", and "Prevention of dementia" and "Overview of homocysteine".)

Recommendations — The optimal dose of folic acid to prevent as many neural tube defects as possible is not precisely known. The United States Preventive Services Task Force recommends a folic acid supplement of 400 micrograms/day (the DV) for all women in the childbearing years [30]. Similarly, the United States National Academies recommend a 400 microgram supplement for such women in addition to the folate in a varied diet (approximately 200 micrograms/day for an average woman). However, doses well above this amount may be necessary to maximally reduce the risk of neural tube defects [9]. We recommend a daily supplement of 400 micrograms in addition to a varied diet for women trying to conceive. Women who have had a previous child with a neural tube defect should consume 4 mg of folic acid starting three months prior to conception and continue this dose at least through the first trimester of pregnancy. (See "Folic acid for prevention of neural tube defects".)

Although the evidence is limited, we recommend not taking supplemental folic acid for the sole purpose of ri cancer. Evidence does not support folic acid supplementation for the purpose of lowering cardiovascular risk (see "Overview of homocysteine").

VITAMIN D — The prevalence of vitamin D deficiency, defined as an elevation in parathyroid hormone concentration that is reversible with vitamin D supplementation, is high in the elderly because of a combination of decreased dietary intake, diminished absorption, and limited exposure to sunlight [31]. Vitamin D deficiency appears to common among other adults as well. In a study of 290 patients hospitalized on a general medical service, vitamin D deficiency was detected in 164 (57 percent), of whom 65 (22 percent) were considered severely deficient (serum concentration of 25-hydroxyvitamin D <8 ng/mL [20 nmol/L]) [32]. Inadequate vitamin D intake, winter seas housebound status were independent predictors of vitamin D deficiency. Even in a subgroup of 77 patients less than age 65 years without known risk factors, the prevalence of vitamin D deficiency was 42 percent.

Osteoporosis — Physiologic doses of vitamin D attenuate bone loss and may decrease fracture rate. Evidence regarding the efficacy and necessary dose of vitamin D to prevent osteoporosis and reduce fracture risk as well as the possible need for concurrent calcium therapy is discussed in detail separately. (See "Calcium and vitamin supplementation in osteoporosis")

As is the case with other vitamins, there is evidence that host factors such as genetic polymorphisms strongly influence fracture risk and may determine the host response to vitamin D. (See "Pathogenesis of osteoporosis")

Falls — Randomized controlled trials of daily vitamin D supplementation (700 to 1000 international units [units]) have shown a decreased risk of falls in the elderly, perhaps through improvements in muscle strength. However, high dose yearly vitamin D (500,000 units) may be associated with an increased risk of falls and fractures in elderly women at high risk of hip fracture. This issue is discussed separately. (See "Prevention of falls and compical falls in older persons", section on 'Vitamin D supplementation' and "Calcium and vitamin D supplementation in osteoporosis", section on 'Efficacy'.)

Extraskeletal outcomes — In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many other cellular functions. Vitamin D deficiency has been implicated as a risk factor for many diseases. However, a causal association between poor vitamin D status and nearly all major diseases (cancer, infections, autoimmune diseases, cardiovascular and metabolic diseases) has not been established. This topic is reviewed in detail separately. (See "Vitamin D and extraskeletal health").

All-cause mortality — Observational studies have found associations between low vitamin D levels and increased all-cause and cardiovascular mortality [33,34]. A meta-analysis of randomized trials of vitamin D supplementa found a decreased risk of all-cause mortality (relative risk 0.93, 95% CI 0.87-0.99) [35]. The underlying were mainly designed to assess fractures, bone density, and falls in older patients. Since mortality was not reported in all such trials, there is the possibility of reporting bias where trials showing a mortality effect would be more likely to include results on mortality.

Recommendations — The Institute of Medicine (IOM) released a report on dietary intake requirements for vitamin D in 2010 [36]. The RDA for vitamin D is 600 International Units (units) for adults through age 70 years and for children 1 to 18 years of age. For adults 71 years and older, 800 units daily is recommended for the prevention of osteoporosis. (See "Overview of vitamin D")
We recommend a daily supplement of 400 to 800 units of vitamin D for the sole purpose of reducing the risk of fractures. Vitamin D deficiency appears to be common among other adults as well. In a study of 290 patients hospitalized on a general medical service, vitamin D deficiency was observed. Inadequate vitamin D intake, winter season, and housebound status were independent predictors of vitamin D deficiency. Even in a subgroup of 77 patients less than 75 years old, high dose yearly vitamin D (500,000 units) may be associated with an increased risk of falls and fractures in elderly women. In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates a variety of biological processes. A meta-analysis of randomized trials of vitamin D supplementation reveals that the underlying trials were mainly designed to assess fractures, bone density, and falls in older patients. Since mortality was not reported in all such trials, there is the possibility of reporting bias where trials showing a mortality effect would be more likely to be detected.
The evaluation and supplementation of vitamin D in patients with vitamin D deficient states and in patients with osteoporosis are discussed elsewhere. (See "Treatment of vitamin D deficiency in adults" and "Calcium and vitamin D supplementation in osteoporosis" and "Vitamin D insufficiency and deficiency in children and adolescents".)

The intake at which the dose of vitamin D becomes toxic is not clear. The IOM has defined the upper limit for vitamin D as 4000 units daily for healthy adults and children 9 to 18 years [36]. This is also the upper limit for pregnant and lactating women. The upper limit for infants and children up to nine years old is lower (table 4) important to inquire about additional dietary supplements (some of which contain vitamin D) that patients may be taking before prescribing supplemental vitamin D. (See "Treatment of vitamin D deficiency in adults", section on 'Dosing'.)

High dose intermittent therapy (100,000 units every four months) is apparently safe and effective [37], but we do not suggest routinely switching patients from daily therapy (600 units). However, it is a reasonable option for patients who are noncompliant with daily therapy. (See "Treatment of vitamin D deficiency in adults".)

Although multivitamins are a convenient and inexpensive way to take vitamin D supplements, many brands contain only 400 units (one DV) and for higher risk patients we suggest a daily intake of 800 units/day to prevent fractures. Thus, patients who take vitamin D supplements because of increased risk of osteoporosis and fractures should either find a multivitamin that contains 800 units or, if they have no reason to supplement other vitamins, take a supplement containing 800 units/day of vitamin D alone; in either case, calcium intake should be supplemented as necessary.

**ANTIOXIDANT VITAMINS** — The antioxidant vitamins include total vitamin A, consisting of preformed vitamin A (retinol) and the carotenoids such as beta-carotene, as well as vitamins C and E. Countless other compounds found in food, especially vegetables and fruits, also have antioxidant properties. A number of studies have examined the hypothesis that antioxidants can prevent cancer and cardiovascular disease by augmenting the body's ability to dispose of toxic free radicals, thereby retarding oxidative damage [38]. (See "Nutritional antioxidants in coronary heart disease".) Retinol may also decrease cancer risk via other mechanisms such as inducing cellular differentiation.

Observational studies have consistently shown that diets high in vegetables and fruits (that are rich in antioxidant vitamins) are associated with a reduced risk of cancer and cardiovascular disease (CVD) [39]. Others have associations between specific vitamins and cancers or cardiovascular disease. However, observational studies may be misleading. The effect may be due to the vitamins themselves, other compounds in vegetables and fruits such as flavonoids, substitution of dietary meat and fat with vegetables and fruits, or healthy lifestyles in people taking antioxidants.

Randomized trials that have examined the role of antioxidant supplements in reducing the risk of cancer and CVD have generally not found positive effects. As an example, a meta-analysis of randomized trials of antioxidant supplements for the prevention of gastrointestinal cancers found no decreased risk with supplementation [40].

While antioxidants are often grouped, specific antioxidant vitamins (including different forms of some vitamins) might be expected to have distinct effects. Individual responses may vary based upon genetic predisposition and other exposures including smoking, dose, and tissue of interest. We will consider the antioxidant vitamins separately, since emerging findings suggest that the specific types of antioxidant vitamins affect cancer and cardiovascular disease differently.

**Vitamin A and the carotenoids** — Total vitamin A consists of preformed vitamin A (retinol) and the carotenoids such as beta-carotene. Retinol is only found in animal products and supplements, while carotenoids that can be converted into vitamin A ("provitamin A carotenoids") are found in fruits and vegetables. (See "Overview of vitamin A".)

**Cancer** — Studies of relationships between vitamin A and carotenoids and cancer have provided mixed results. Results of observational studies and clinical trials have not been consistent, limiting our ability to make conclusive recommendations.

- Two large, randomized, placebo-controlled trials assessed the effects of beta-carotene on risk of lung among men at increased risk for lung cancer because of smoking or asbestos exposure [41,42]. Both statistically significant increases in lung cancer risk among men who received the supplements. The excess risk appears to resolve over time once supplements were stopped [43]. (See "Chemoprevention of lung cancer", section on 'Primary chemoprevention'.)

- The Physicians Health Study found that 12 years of beta-carotene supplements (50 mg every other day
Calcium and vitamin D deficiency. This is also the upper limit for table 4. It is in Treatment of vitamin D deficiency in adults, section on calcium, but we do only 400 units (one DV) and for higher risk patients we suggest a daily intake of 800 units/day to prevent fractures. Countless other compounds found in vegetables and fruits such as carotenoids have been shown to have antioxidant activity. Others have shown that vitamin E and vitamin C supplements (50 mg every other day) are effective in reducing the risk of lung cancer. Overall, the evidence is conflicting and is not based on robust statistical analysis.
produced neither benefit nor harm with respect to the incidence of malignant neoplasms [44]. Overall, the cohort was at low risk for lung cancer since few smoked. The Women's Health Study also found no effects [43].

- The ATBC Cancer Prevention Study showed an increase in both prostate cancer incidence and mortality (23 and 15 percent, respectively) among subjects randomized to beta-carotene [41]. The excess risk appeared to resolve over time once supplements were stopped [43].

- An analysis of 7627 women who were free of cancer at random assignment in the Women's Antioxidant Cardiovascular Study found that after a mean follow-up of 9.4 years, beta-carotene 50 mg every other day had no effect on the incidence of cancer (relative risk 1.00, 95% CI 0.85-1.17) [46].

- Observational studies of vitamin A (or carotenoid) intake and breast cancer have yielded varying results. In the Iowa Women's Health Study, no association between dietary vitamin A and breast cancer was observed [47]. In contrast, evidence from the Nurses' Health Study has suggested that high intake of carotenoids may decrease the risk of breast cancer [48,49]. This association may be strongest in premenopausal women with a positive family history who appear to have significant reductions in breast cancer risk with increasing dietary alpha-carotene, beta-carotene, lutein/zeaxanthin, and total vitamin A [49]. Similarly, another report from the Nurses' Health Study found a decreased risk of breast cancer in women with higher plasma levels of carotenoids [50]. There are no clinical trials of vitamin A intake and breast cancer.

- Results from a four-year clinical trial of antioxidants to prevent colorectal adenoma were also disappointing [51]. The Polyp Prevention Study Group reported no reduction in adenoma risk in 864 patients randomized to receive either beta-carotene (25 mg daily), vitamin C (1 g daily) and E (400 mg daily), or both beta-caroter and vitamins C and E.

Possible explanations for discordant results for observational and experimental studies with regard to vitamin A and carotenoids and cancer risk include the inability of observational data to completely control for confounding by other healthy behaviors, differences in form or dose of vitamins, and interaction with other exposures such as tobacco [52]. The increase in risk of lung cancer in two RCTs of beta-carotene has dampened enthusiasm for further trials of antioxidants to prevent cancer [41,42]. There is currently no strong evidence that vitamin A and carotenoids supplements reduce the risk of cancer.

Cardiovascular disease— Randomized trials of vitamin A and beta-carotene have shown no benefit for primary or secondary prevention of coronary heart disease (CHD) and one suggested potential harm [53]. This is discussed detail elsewhere. (See "Nutritional antioxidants in coronary heart disease".)

Immunity — Vitamin A improves immunity in children living in developing countries where dietary intake is inadequate and life-threatening infectious diseases are common. A meta-analysis of 12 controlled trials of vitamin A showed a 30 percent reduction in overall mortality, with a 61 percent reduction in mortality among hospitalized patients with measles. One United States study of children with measles showed more severe illness in children with lower serum retinol levels [54]. The World Health Organization recommends community-based Vitamin A supplementation in developing countries even in the absence of signs and symptoms of deficiency [55]. There is no reason to expect an improvement in immunity with vitamin A supplementation in people who already have adequate dietary intake.

Fractures — There is consistent evidence from observational studies that vitamin A intake (specifically retinol) within the range taken by many people in Western societies is a risk factor for osteopenia and fractures [56]. An example, 72,337 postmenopausal women age 34 to 77 years were followed for 18 years in the Nurses Health Study [57]. Women in the highest quintile of total vitamin A intake had a relative risk for hip fracture of 1.48 compared with women in the lowest quintile. This increased risk was attributed primarily to retinol. An earlier Finns cohort study had similar findings [56]. Thus, patients should be cautioned against diets high in retinol (preformed vitamin A), especially if they have other risk factors for osteopenia, and should avoid vitamin A supplements, including multivitamins containing preformed vitamin A, if their dietary intake is high. Common food sources of preformed vitamin A include liver, milk, egg yolk, and butter. (See "Drugs that affect bone metabolism", section 'Vitamin A and synthetic retinoids'.)

Cataracts — Some studies have suggested that individual or multivitamin supplements containing vitamin A might reduce the risk for developing cataracts. This is discussed in detail separately. (See "Cataract in adult section on 'Vitamin supplementation'.")

Recommendations — Beta-carotene supplement use should be discouraged based upon its lack of clinical efficacy and possible adverse effects with respect to both cardiovascular and cancer risk.
Overall, the excess risk appears to be greatest in women younger than 70 years of age who had taken the 50 mg every other day had a 47% reduction in breast cancer risk compared with women in the lowest quintile. This increased risk was attributed primarily to retinol. An earlier Finnish study also found a similar decrease in breast cancer risk in women who had taken vitamin A supplements. Thus, patients should be cautioned against diets high in retinol (preformed vitamin A).

Observational studies of vitamin A (or carotenoid) intake and breast cancer have yielded varying results. In a study of premenopausal women, there was a significant inverse association with increasing dietary alpha-tocopherol, beta-carotene, and vitamin C. A recent meta-analysis of 11 prospective studies also found a significant inverse association with increasing dietary alpha-tocopherol and betacarotene, and vitamin C. Similarly, another report from the Nurses' Health Study showed a significant inverse association with increasing dietary alpha-tocopherol, beta-carotene, and vitamin C.

There is currently no strong evidence that vitamin A and carotenoids are protective against breast cancer. A number of studies have shown no benefit for primary or secondary prevention of breast cancer. This is discussed in detail in the section on "Drugs that affect bone metabolism," section on "Cataract in adults," and in "its".
A diet with at least five servings of fruits and vegetables per day is prudent and is likely to provide an optimal distribution of carotenoids and the best opportunity to prevent several common cancers without risk of unintentional harm. Vegetarians, including vegans, do not need to take vitamin A supplements if they eat an adequate variety of vegetables containing carotenoids. Supplementation with vitamin A at the community level in poor countries is recommended by the World Health Organization. We do not recommend vitamin A supplementation for the purpose of preventing cardiovascular disease or cancer.

**Vitamin E** — Vitamin E is a family of related chemicals. Typical dosing is given in terms of alpha-tocopherol. The conversion is: 15 mg of alpha-tocopherol is the equivalent of 22 units of natural vitamin E or 33 units of synthetic vitamin E.

**Cancer** — Observational studies have found variable effects of vitamin E on certain cancers, particularly within subgroups such as smokers [47-49, 59-61], but randomized trials do not support a protective effect.

Randomized trials of vitamin E in cancer prevention include:

- The Women's Health Study followed 39,876 apparently healthy women ages 45 and older for a mean of 10.1 years [62]. Compared with placebo, supplementation with 600 units of natural-source vitamin E on alternate days had no effect on the incidence of all cancer (relative risk (RR) 1.01, 95% CI 0.94-1.08) or on breast cancer (RR 1.00), lung cancer (RR 1.09), colon cancer (RR 1.00), or cancer death (RR 1.12).

- The Polyp Prevention Study observed no reduction in colorectal polyps among subjects randomized to receive vitamin E [51].

- The HOPE-TOO trial found no effect of vitamin E supplementation (400 units daily) on cancer incidence or cancer deaths after a median follow-up of seven years [63].

- An analysis of 7627 women who were free of cancer at random assignment in the Women's Antioxidant Cardiovascular Study found no effect of vitamin E (600 units every other day) on the incidence of cancer after a mean follow-up of 9.4 years [46].

In contrast to these negative trials, the ATBC Cancer Prevention Study observed a 32 percent decrease in prostate cancer incidence and a 41 percent decrease in prostate cancer mortality among men randomized to 50 mg (75 units) of alpha-tocopherol (vitamin E) for five to eight years compared with placebo [64].

However, subsequent large randomized trials found no reduction in prostate cancer incidence with vitamin E supplementation:

- The SELECT trial followed 35,533 men (ages 50 and older for African American men and ages 55 and older for other men) for a median of 5.5 years [65]. Compared with placebo, vitamin E supplementation (400 units daily) had no effect on rates of prostate cancer (hazard ratio [HR] 1.13, 95% CI 0.95-1.35) or total cancer (HR 1.03, CI 0.91-1.17).

- The Physicians' Health Study II followed 14,641 male physicians ages 50 and older for an average of 8.0 years [66]. Compared with placebo, vitamin E supplementation (400 units every other day) had no effect on the incidence of prostate cancer (HR 0.97, CI 0.85-1.09) or total cancer (HR 1.04, CI 0.95-1.13).

Supplementation with vitamin E does not appear to be beneficial in preventing cancer.

**Cardiovascular disease**— Nearly all randomized trials of vitamin E have shown no benefit for primary or secondary prevention of CHD [53]. Additionally, vitamin E supplementation may increase the risk of heart failure [63].

**Stroke** — The best available evidence does not suggest that vitamin E supplements protect against stroke.

- The Health Professionals Follow-up Study, an observational study including 43,738 men, showed no association between supplemental vitamin E (250 units or more daily) and stroke risk [67].

- In the Heart Outcomes Prevention Evaluation (HOPE) trial, as well as its extension HOPE-TOO, supplementation with vitamin E (400 units daily) had no significant effect on the risk of stroke [63].

- In the randomized ATBC study, which followed 22,271 male smokers for a median of six years, supplementation with vitamin E 50 mg (75 units) had no overall effect on stroke risk. However, in a subgroup analysis, vitamin E increased the risk for subarachnoid hemorrhage and decreased the risk for ischemic stroke.
distribution of carotenoids and the best opportunity to prevent several common cancers without risk of unintentional
recommended by the World Health Organization. We do not recommend vitamin A supplementation for the purpose
Cardiovascular Study found no effect of vitamin E (600 units every other day) on the incidence of cancer after a
]. Compared with placebo, vitamin E supplementation (400 units daily)
]. Compared with placebo, vitamin E supplementation (400 units every other day) had no effect on the
— Nearly all randomized trials of vitamin E have shown no benefit for primary or secondary
]. These
particularly in men with hypertension [68].

- A six-year randomized trial of daily supplementation with vitamin E (136 units) and vitamin C (250 mg slow release) in 520 people showed a statistically significant improvement in the average annual increase in carotid artery intima-media thickness compared with placebo (.010 mm versus .014 mm) [69]. The clinical implications of this are unclear. In contrast, in a substudy of 732 high-risk patients from the HOPE trial, supplementation with vitamin E had no effect on progression of carotid intimal medial thickness over an average follow-up of 4.5 years [70].

**Dementia** — Although observational studies suggested that increased dietary intake of vitamin E or vitamin E supplementation might protect against the development of Alzheimer disease and vascular dementia [71-73], randomized trials vitamin E supplementation does not appear to affect the risk of dementia [74,75]. (See "Prevention of dementia", section on 'Antioxidant vitamins'.)

**Infection** — Several studies have reported that supplementation with vitamin E improves the immune response [76,77]. Such an effect is of particular interest in elderly people, in whom an age-related decline in immune response may increase the risk of infections and their complications.

However, clinical trials that have examined the use of vitamin E to prevent infections in the elderly have not found clinical benefits. Large, randomized, placebo-controlled studies found no reduction in the incidence of respiratory infections when either institutionalized [78,79] or noninstitutionalized [80] elderly patients received daily vitamin E supplements. Furthermore, in the study in the noninstitutionalized elderly, among patients experiencing a respiratory infection, those who received vitamin E (200 units per day) had a significantly longer total illness duration (19 versus 14 days), more symptoms, and a higher frequency of fever and activity restriction [80].

**Venous thromboembolism**— High doses of vitamin E may interfere with vitamin K and affect coagulation. (See "Overview of vitamin E", section on 'Excess and toxicity'.)

A secondary analysis from the Women's Health Study found that women randomly assigned to receive 600 units of vitamin E every other day had a lower risk of venous thromboembolism (VTE) than women receiving placebo (hazard ratio 0.79, 95% CI 0.66-0.94) [81]. This effect needs to be confirmed in other randomized trials before vitamin E can be recommended for prevention of VTE.

**All-cause mortality** — A meta-analysis of randomized trials of vitamin E supplementation (many of which are discussed individually above) examined the effects of supplementation on all-cause mortality [82]. There significant effect on mortality across all trials; however, mortality was increased in patients who received high-dose vitamin E supplementation (≥400 units/day) (increase in mortality of 39 per 10,000 persons, 95% CI 3-74 per 10,000 persons). There appeared to be a dose-response relationship. As a whole, patients treated with low-dose supplementation had a decrease in mortality; however, trials of these doses were often performed in malnourished populations or used other supplements in combination with vitamin E. A number of the trials of high-dose supplementation were in patients with chronic diseases, and it is unclear whether the observed harm from such supplementation would carry over to a healthier population.

Similar to the overall results of the above analysis, a meta-analysis that did not stratify trials by dose of vitamin E found no significant effect of supplementation on all-cause mortality [53].

**Recommendations** — Supplementation with vitamin E does not appear to be beneficial in preventing cancer. We do not recommend supplementation for this purpose, particularly given the possible increase in all-cause mortality with doses ≥400 units/day.

With respect to cardiovascular disease prevention, randomized trials provide strong evidence against a benefit for supplementation with vitamin E for primary and secondary prevention of CHD. (See "Nutritional antioxidants coronary heart disease".) In 1999 the American Heart Association recommended that the most prudent and scientific approach for the general population is to consume a balanced diet with emphasis on fruits, vegetables, and whole grains [83].

We do not recommend high-dose vitamin E for the prevention of Alzheimer disease or infections. Since the best available evidence, while not conclusive, suggests that high-dose vitamin E (≥400 units/day) might increase all-cause mortality, patients without special indications should not take supplements containing high doses of vitamin E for preventive health care. In addition, individuals taking anticoagulants should be particularly advised against high doses of vitamin E because of the synergistic action of vitamin E with these drugs. The Upper Limit of vitamin E according to the United States National Academies is 1000 mg/day as alpha-tocopherol.
Supplementation with vitamin E had no effect on progression of carotid intimal medial thickness over an average 7.7 years. Several studies have reported that supplementation with vitamin E improves the immune response. Elderly patients received daily vitamin E without a clear benefit. High doses of vitamin E may interfere with vitamin K and affect coagulation. (See Table 2.) A study showed that vitamin E every other day had a lower risk of venous thromboembolism (VTE) than women receiving placebo (hazard ratio: 0.67). This effect needs to be confirmed in other randomized trials before vitamin E can be recommended for prevention of VTE.

Supplementation with vitamin E does not appear to be beneficial in preventing cancer. We do not recommend supplementation for this purpose, particularly given the possible increase in all-cause mortality with vitamin E supplementation. A scientific approach for the general population is to consume a balanced diet with emphasis on fruits, vegetables, and whole grains.
Vitamin C

Cancer — There is little evidence to support an important role for vitamin C in cancer prevention [84]:

- The Physicians' Health Study II randomly assigned 14,641 male physicians ages 50 and older to vitamin C 500 mg daily or placebo [66]. After an average follow-up of 8.0 years, vitamin C had no effect on the incidence of cancer (hazard ratio 1.01, 95% CI 0.92-1.10).

- An analysis of 7627 women who were free of cancer at random assignment in the Women's Antioxidant Cardiovascular Study found that after a mean follow-up of 9.4 years, vitamin C 500 mg daily had no effect on the incidence of cancer (relative risk 1.11, 95% CI 0.95-1.30) [46].

Cardiovascular disease— Randomized trials have shown no benefit of vitamin C for primary or secondary prevention of coronary heart disease (CHD). This is discussed in detail elsewhere. (See "Nutritional antioxidants in coronary heart disease".)

Stroke — The Health Professionals Follow-up Study, an observational study including 43,738 men, showed no association between supplemental vitamin C (700 mg or more daily) and stroke risk [67].

A six-year randomized trial of supplemental vitamin C and vitamin E in 520 people showed a statistically significant improvement in the average annual increase in carotid artery intima-media thickness compared with placebo (.010 mm versus .014 mm) [69]. The clinical implications of this are unclear.

Cataracts and macular degeneration— Some studies have suggested that individual or multivitamin supplements containing vitamin C might reduce the risk for developing cataracts or macular degeneration. These issues are discussed in detail separately. (See "Cataract in adults", section on 'Vitamin supplementation' and "Age-related macular degeneration: Treatment and prevention", section on 'Nutritional and vitamin supplements'.)

Recommendations — We do not recommend supplemental vitamin C for the primary or secondary prevention of CHD (see "Nutritional antioxidants in coronary heart disease"), or for cancer prevention. Evidence that vitamin C decreases eye diseases are not strong or consistent enough to recommend supplements for this purpose.

VITAMIN B6 (PYRIDOXINE) — Vitamin B6 is thought to reduce the risk of cardiovascular disease and cancer. However, it has been difficult to separate out the effects of vitamin B6 from that of other vitamins and of other substances in fruits and vegetables, and the optimal dose is not well-characterized [85].

High levels of homocysteine are associated with an increased risk of cardiovascular disease. Supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels. However, randomized controlled trials of supplementation for secondary prevention do not support the hypothesis that these vitamins are beneficial for cardiovascular disease. This is discussed in detail elsewhere. (See "Overview of homocysteine".)

Vitamin B6 may lower risk of colorectal cancer. Possible mechanisms include preventing abnormalities in DNA synthesis, repair, and methylation [86]. In a meta-analysis of nine prospective studies, vitamin B6 intake and blood levels of pyridoxal 5'-phosphate (the active form of vitamin B6) were inversely associated with risk of colorectal cancer [87].

A nested case-control analysis from the Nurses' Health Study cohort found a trend toward a lower risk of breast cancer in women with higher plasma levels of vitamin B6 [88]. Comparing the highest with the lowest quintile plasma vitamin B6 levels, the relative risk was 0.70 (95% CI 0.48-1.02).

Recommendation — Current evidence does not support vitamin B6 supplementation, alone or in combination with vitamin B12 and folic acid, for the purpose of lowering cardiovascular risk. (See "Overview of homocysteine".)

Although higher plasma levels of vitamin B6 are associated with lower cancer risk, it is unclear whether supplementation with vitamin B6 is beneficial in cancer risk reduction.

VITAMIN B2 (RIBOFLAVIN) — Although overt riboflavin deficiency is rare, one study showed a benefit of supplementation with a very large dose in preventing migraine [89]. (See "Preventive treatment of migraine in adults", section on 'Riboflavin'.)

Recommendation — There is no strong evidence that supplemental vitamin B2 is helpful in healthy people eating a usual American diet.

VITAMIN B12

Vitamin B12 deficiency is associated with several disease states:
After an average follow-up of 8.0 years, vitamin C had no effect on the incidence of...
• Severe vitamin B12 deficiency causes neurologic disease and megaloblastic anemia. (See "Etiology and clinical manifestations of vitamin B12 and folic acid deficiency".

• Subtle B12 deficiency, even without anemia, may account for some cases of dementia [90, 91]. It may account for deteriorating balance in some elderly people, but this hypothesis has not been well studied.

• Vitamin B12 deficiency may also be an important cause of hyperhomocysteinemia, particularly in the elderly [90]. High levels of homocysteine are associated with an increased risk of cardiovascular disease. Supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels, but randomized trial data do not support the hypothesis that these vitamins prevent cardiovascular disease; some trials suggest harm. This is discussed in detail elsewhere. (See "Overview of homocysteine".)

Hyperhomocysteinemia is also associated with osteoporosis; it is not known whether this association is causal or whether lowering homocysteine levels would affect risk, however supplementation with folate and vitamin B12 in high risk groups may reduce the risk of fractures. (See "Overview of the management of osteoporosis in postmenopausal women", section on 'Folate/vitamin B12'.)

Suboptimal vitamin B12 status is most commonly caused by poor absorption coupled with inadequate intake. Malabsorption of cobalamin in food is primarily the result of an inability to release cobalamin from dietary proteins, especially in the presence of reduced gastric acid secretion. In the elderly, gastric atrophy and hypochlorhydria result in reduced gastric acid and less efficient absorption of vitamin B12 from foods in particular [92]; th decrease in absorption is likely to be a far more common cause of vitamin B12 deficiency than pernicious anemia. Patients with food cobalamin malabsorption will still be able to absorb low dose crystalline vitamin B12 found in supplements [93] (See "Etiology and clinical manifestations of vitamin B12 and folic acid deficiency".).

Patients with poor intake, including vegans, alcoholics, and people with little dietary variation (including the elderly) are also prone to B12 deficiency. Patients having undergone gastric or ileal resection have traditionally been treated with intramuscular vitamin B12, since oral supplementation at usual doses does not allow adequate B12 absorption. However, some studies suggest that high-dose (1000 to 2000 micrograms daily) oral supplementation is efficacious in treating vitamin B12 deficiency even in this subgroup of patients. A secondary transport system (independent of intrinsic factor) provides adequate absorption at these levels. (See "Diagnosis and treatment vitamin B12 and folic acid deficiency".)

Physiologic deficiency of vitamin B12 can be measured by the level of methylmalonic acid, which rises with low intake and falls with supplementation. The prevalence of B12 deficiency in the elderly by this definition, even with "normal" serum levels, may be high, 82 percent in one study of 285 elderly people [94].

**Recommendations** — Given the high prevalence of vitamin B12 deficiency in the elderly, and the safety of supplementation, we recommend a supplement of 2.4 micrograms (100 percent of the RDA) in older adults. In the elderly or other populations with a high prevalence of atrophic gastritis, vegan populations, patients who have had gastric bypass surgery, alcoholics, and others with poor dietary variation, this dose may be inadequate. However, there are few studies to guide dosing in these individuals. One randomized trial suggested that doses higher than 5 micrograms/day may be required in order to normalize serum B12 levels in the elderly [95]. There is no known toxicity of vitamin B12 at these doses, and the Upper Limit of vitamin B12 intake is not defined. In these high risk populations, it is reasonable to periodically monitor the adequacy of replacement with a test such as serum methylmalonic acid or B12 level. (See "Diagnosis and treatment vitamin B12 and folic acid deficiency".)

**TOXICITY AT HIGH DOSES** — Potentially toxic levels of vitamins can be achieved easily in people who take very high potency vitamins, which can be obtained in specialty stores, over the Internet, and even in pharmacies. High doses can also be achieved by taking a large number of pills even if the dose per pill is not extraordinary.

Water soluble vitamins have an extraordinarily broad therapeutic ratio, with toxicity occurring only at doses thousands of times the RDA. It has been hypothesized that large doses of vitamin C may increase the risk of kidney stones by increasing oxalate excretion, but this remains controversial. (See "Risk factors for calcium stones adults".)

Fat soluble vitamins are generally more toxic than water soluble vitamins. Vitamin D may cause hypercalcemia at doses as low as 2000 units/day (recommended upper limit) in some people. Vitamin A in pregnancy is teratogenic at doses as low as several times the RDA (with an apparent threshold at 10,000 units/day of supplemental vitamin A) [96]. Beta-carotene appears to increase the risk of lung cancer in adults who are otherwise at high risk because of smoking or exposure to asbestos. As discussed above, there are concerns that vitamin E supplementation above 400 units per day may be associated with increased all-cause mortality. (See 'All-cause mortality' above.)
Etiology and It may also, vitamin B6, and vitamin B12 can lower homocysteine levels, but randomized patients with poor intake, including vegans, alcoholics, and people with little dietary variation (including the elderly) diagnosis and treatment of there are few studies to guide dosing in these individuals. One randomized trial suggested that doses higher than 50. There is no known th of thousands of times the RDA. It has been hypothesized that large doses of vitamin C may increase the risk of kidney factors for calcium stones in. BetaVcarotene appears to increase the risk of lung cancer in adults who are otherwise at high risk because own .) in .) .) .)
**MULTIVITAMINS**

**Rationale** — The rationale for a daily multivitamin for adults is based on known or potential effectiveness for some of the component vitamins coupled with relative safety in low (0.5 to 1.5 of the RDA) doses, low cost, and the efficiency of taking just one pill.

This rationale is changing as more randomized trials of vitamin supplements are reported, many of which have not supported the protective effect suggested by observational studies [97].

**Contents** — In the United States, the federal government does not regulate food supplements (vitamins, minerals, and herbs) to assure safety and efficacy. However, manufacturers are required to list contents in a standard way, making it easier for consumers to compare brands.

Multivitamins are sold in a dazzling array of combinations and doses. Therefore, the patient must review the label to be sure what he or she is taking.

Most "ordinary", brand-name and generic, relatively inexpensive multivitamins sold in United States pharmacies contain at least one RDA of all of the major vitamins, including vitamin D, vitamins B6 and B12, folic acid, vitamin E; the dose of vitamin E, generally 15 mg, is well below the level shown to be efficacious or harmful in the studies described above. Many multivitamins contain minerals as well, but the dose of calcium and iron is well below one DV. The cost of one simple multivitamin per day is as low as $15 to $35 per year.

**Efficacy**

- Vitamin D deficiency is common in many populations, and supplements of vitamin D with calcium have been shown to reduce fracture rates and falls.
- Vitamin B12 deficiency in the elderly may account for some cases of neurologic disease (dementia, poor balance).
- Folate intake from the diet is inadequate to prevent neural tube defects in many women, and these defects occur before pregnancy is detected in most women.

High levels of homocysteine are associated with an increased risk of cardiovascular disease. Supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels. However, randomized, controlled trials of supplementation for secondary prevention do not support the hypothesis that these vitamins are beneficial for cardiovascular disease. This is discussed in detail elsewhere. (See "Overview of homocysteine".)

An observational study of 161,808 women with prospective data collection and a median follow-up of approximately 8 years found no association between multivitamin use and risk of cancer, cardiovascular disease, or death [96].

**Safety** — Most common, brand-name multivitamins and many generics contain 50 to 150 percent of the RDA for all vitamins. Some may have lower amounts of vitamin K, however this vitamin is synthesized by bacteria in the gut. Some may contain several times the RDA of vitamin B12, which is harmless even at much higher doses.

In this dose range, multivitamins are apparently safe for most adults. The dose of vitamin E is well below the levels reported to cause an increase in overall mortality, and the dose of beta-carotene, usually a part of the total A activity, is well below levels associated with lung cancer. The dose of folic acid is also lower than that found in a randomized trial to potentially increase cancer risk.

Water soluble vitamins have an extraordinarily broad therapeutic ratio, with toxicity occurring only at doses thousands of times the RDA. Fat soluble vitamins are generally more toxic than water soluble vitamins. (See 'Toxicity at high doses' above.)

Some individuals may be harmed by even ordinary doses of vitamin A. Vitamin A has been shown in observational studies to be a risk factor for osteopenia and fractures in the range ingested by a substantial proportion of the adult population in the US. People at increase risk of osteopenia (see "Screening for osteoporosis", section on 'Risk factor screening'), or with relatively high dietary intake of vitamin A, should not take additional supplements of this vitamin until further research clarifies whether the association between vitamin A and osteopenia is causal (see 'Fractures' above). Additionally, vitamin A is teratogenic starting at doses of only 10,000 units/day of supplementation (see 'Toxicity at high doses' above).

Manufacturers have been reducing the amount of vitamin A in multivitamins, but supplementation, even at less than 100 percent of the RDA, does not seem prudent in people who are otherwise at increased risk.

**TESTING FOR VITAMIN DEFICIENCY** — Blood tests for many vitamins are widely available. Fueled by popular bel
The rationale for a daily multivitamin for adults is based on known or potential effectiveness for some of the commonly deficient nutrients. Multivitamins are sold in a dazzling array of combinations and doses. Therefore, the patient must review the label to ensure it contains the nutrients he or she requires. An observational study of 161,808 women with prospective data collection and a median follow-up of approximately 9.8 years has shown that the most common, brand-name multivitamins and many generics contain 50 to 150 percent of the RDA for all of the micronutrients, usually a part of the total vitamin ingested by a substantial proportion of the adult population. An observational study to be a risk factor for osteopenia and fractures in the range ingested by a substantial proportion of the adult population. Manufacturers have been reducing the amount of vitamin A in multivitamins, but supplementation, even at less than 98 percent of the RDA, can be beneficial. Blood tests for many vitamins are widely available. Fueled by popular belief
in the importance of vitamins and by commercial interests, testing is being promoted to detect unrecognized
deficiency and to tailor supplements to individual needs. This practice seems unwarranted in most patients for
several reasons:

- There is insufficient information about the optimum blood levels of vitamins, making it difficult to interpret
  subtle deficiency states.
- Many people ingest too little of some vitamins, such as folate and vitamins D and B12, and so should take
  supplements in any case.

Testing for specific deficiencies in clinical situations where they are suspected (eg, elderly patients with
osteoporosis or evaluation of anemia in alcoholic patients) remains appropriate.

Additional information about polymorphisms, which increase requirements for specific vitamins, is likely to become
available. As noted earlier, this appears to be the case for genes controlling the metabolism of folate and vitamin D.
However, there is currently not enough understanding of individual risk to warrant routine testing for vitamin levels
or testing for polymorphisms.

SPECIAL DIETS — People on restricted or special diets may have additional needs for vitamin supplementation. As
an example, adequate vitamin B12 levels are strongly affected by dietary intake in addition to absorption. In
younger adults, low consumption of animal-source food is the main cause of low vitamin B12 levels; in older adults,
alabosorption of vitamin B12 from food is the most common cause [99]. The lowest intakes of vitamin B12 a in
those who eat no animal products, and intake increases with increasing intake of animal source foods [99].

Some special diets include (see "Vegetarian diets for children"):

- Semivegetarian — Meat occasionally is included in the diet. Some people who follow such a diet may not eat re
  meat but may eat fish and perhaps chicken.
- Lactoovovegetarian — Eggs, milk, and milk products (lacto = dairy; ovo = eggs) are included, but no meat is
  consumed.
- Lactovegetarian — Milk and milk products are included in the diet, but no eggs or meat are consumed.
- Macrobiotic — Whole grains, especially brown rice, are emphasized and vegetables, fruits, legumes, and
  seaweeds are included in the diet. Locally-grown fruits are recommended. Animal foods limited to white meat c
  white-meat fish may be included in the diet once or twice a week.
- Vegan — All animal products, including eggs, milk, and milk products, are excluded from the diet. Some vegans
  do not use honey and may refrain from using animal products such as leather or wool. They also may avoid
  foods that are processed or not organically grown.

People who consume a vegan diet should be supplemented with vitamin B12 (at the RDA of 2.4 micrograms/day) if
they do not consume other fortified food products (such as cereals). They are also at risk for inadequate vitamin
D status and should consider a supplement, particularly during winter months [101].

Lactoovovegetarians and lactovegetarians should also consider supplementation with vitamin B12. In contrast,
people consuming a very low carbohydrate diet (eg, "Atkins" style) may consume few fruits and vegetables,
particularly during the initial phase. Although there is little evidence about serum vitamin concentrations in these
situations, at least one study showed increased serum B12 levels and no change in serum folate [102].

There are many other specialized diets that have not been adequately researched for their nutritional effects.
Because most of the vitamins are available in a variety of foods, diets excluding one specific food generally would
not be expected to result in deficiency or need for supplementation. In contrast, people who restrict entire
categories of foods or consume only a few types of specific foods or groups may be at risk for deficiency of specific
vitamins. Reasonable options in such patients are to recommend a daily multivitamin or consider specific testing
(eg, 25-OH-vitamin D levels) based on the expected nutrient deficiencies in the diet.

People in other groups with "poor" diet and little dietary variety (alcoholics, populations living in poverty), may also
benefit from a daily multivitamin, although this may be difficult to implement in such patients.

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "Patient
information: Calcium and vitamin D for bone health") We encourage you to print or e-mail these topics, or to refer
patients to our public web site, www.uptodate.com/patients, which includes these and other topics.
available. As noted earlier, this appears to be the case for genes controlling the metabolism of folate and vitamin D. — People on restricted or special diets may have additional needs for vitamin supplementation. As younger adults, low consumption of animal-source food is the main cause of low vitamin B12 levels; in older adults, the lowest intakes of vitamin B12 are seen.

Semivegetarian — Meat occasionally is included in the diet. Some people who follow such a diet may not eat red meats, and many eat fish and shellfish instead. Local-grown fruits are recommended. Animal foods limited to white meat or cheese are included in the diet.

Vegan — All animal products, including eggs, milk, and milk products, are excluded from the diet. Some vegans also avoid foods that are processed with rennet, which is derived from animal stomachs.

Patient (00). We encourage you to print or e-mail these topics, or to refer...
RECOMMENDATIONS—The second United States Preventive Services Task Force (USPSTF), published in 1996, recommends a folic acid supplement of 400 micrograms/day for all women in the childbearing years [30]. USPSTF found insufficient evidence to recommend for or against the use of supplements of vitamins A, C, E, multivitamins with folate, or antioxidant combinations for the prevention of cancer or cardiovascular disease and recommended against the use of beta-carotene supplements for these purposes [103]. The USPSTF clinical practice guideline for routine vitamin supplementation to prevent cancer and cardiovascular disease, as well as other USPSTF guidelines, can be accessed through the website for the Agency for Healthcare Research and Quality at www.ahrq.gov/clinic/uspsfix.htm.

Because of newer evidence, especially randomized trials, current recommendations are more complex and involve more individual tailoring than was justified just a few years ago [104,105]. In general, simple multivitamins (containing 0.5 to 1.5 RDA of all vitamins) are probably not beneficial for most adults who eat a balanced diet and get regular sun exposure or drink vitamin D-fortified dairy products. Because multivitamins may be harmful in some people, vitamin recommendations should be tailored to individual patients:

- A diet with five to nine servings of vegetables and fruits per day supplants multivitamin use in most patients. This diet promotes health not only by providing known vitamins, but also because it contains fiber and other less well-defined nutrients and replaces meat and animal fat.
- Women of childbearing potential should take a vitamin supplement containing at least 400 micrograms of acid per day. In addition to a varied diet, women who are trying to conceive should take a daily supplement of 400 to 800 micrograms folic acid or a prescription prenatal vitamin.
- People with diets high in vitamin A, pregnant women, and those who are at increased risk for fractures or osteopenia should avoid supplements that contain vitamin A, including multivitamin supplements. Prescription prenatal vitamins in the US have reduced amounts of vitamin A and increased folic acid (usually 800 micrograms).
- The RDA for vitamin D is 600 International Units (units) for adults through age 70 years and for children 1 to 18 years of age. For adults 71 years and older, 800 units daily is recommended. (See "Overview of vitamin D".) Since the best available evidence, while not conclusive, suggests that high-dose vitamin E (≥400 International Units/day) increases all-cause mortality, patients without special indications should not take supplements containing high doses of vitamin E for preventive health care. Additionally, patients on anticoagulants should be particularly discouraged from using very high doses of vitamin E supplementation, which might cause bleeding complications.
- Patients with clinical reasons for vitamin deficiency, such as those with alcoholism, malabsorption, vegan diet, a history of gastric bypass surgery, or some inborn errors of metabolism, as well as those being treated with hemodialysis or parenteral nutrition, should receive multivitamin supplements whether or not blood tests suggest deficiency.
- Blood tests for vitamin deficiency are useful in some patients with clinical indications. Marginal blood levels should not be overinterpreted as abnormal. Patients with clear-cut deficiencies should be treated with additional vitamins as indicated.
- Patients should not use large doses of individual vitamins. While they may take multivitamins tailored to age, sex, or specific medical conditions, with the exception of pregnancy this is not supported by strong evidence and may be harmful.
- Clinicians should encourage their patients to take the vitamins that are known to be effective while avoiding doses that are toxic. They should also be interested in and nonjudgmental about a wide range of behaviors between these extremes, so that patients will be willing to share their beliefs and information about the use of vitamins and other "alternative" treatments.

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REFERENCES

The third

- Get regular sun exposure or drink vitamin D-fortified dairy products. Because multivitamins may be harmful in some

- Folic acid (folic acid) containing high doses of vitamin E for preventive health care. Additionally, patients on anticoagulants should be

- Amin D"__

- ____)
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Yaffe K, Clemons TE, McBee WL, et al. Impact of antioxidants, zinc, and copper on cognition in the elderly: a
Girodon F, Galan P, Monget AL, et al. Impact of trace elements and vitamin supplementation on immunity and


101. Outila TA, Kärkkäinen MU, Seppänen RH, Lamberg-Allardt CJ. Dietary intake of vitamin D in premenopausal, healthy vegans was insufficient to maintain concentrations of serum 25-hydroxyvitamin D and intact parathyroid hormone within normal ranges during the winter in Finland. J Am Diet Assoc 2000; 100:434.


GRAPHICS
Homocysteine is metabolized by one of two divergent pathways: transsulfuration; and remethylation. The transsulfuration of homocysteine to cysteine is catalyzed by cystathionine-β-synthase (CBS), a process that requires pyridoxal phosphate (vitamin B6) as a cofactor. Remethylation of homocysteine produces methionine. This reaction is catalyzed either by methionine synthase or by betaine-homocysteine methyltransferase. Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase.

### Vitamin deficiency syndromes

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Deficiency syndrome</th>
<th>Main symptoms/signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Xerophthalmia</td>
<td>Dry eyes and skin, blindness</td>
</tr>
<tr>
<td>D</td>
<td>Rickets, osteomalacia</td>
<td>Bone deformity</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>Anemia</td>
</tr>
<tr>
<td>K</td>
<td></td>
<td>Bleeding diathesis</td>
</tr>
<tr>
<td>C</td>
<td>Scurvy</td>
<td>Capillary fragility, bleeding</td>
</tr>
<tr>
<td>Thiamine (B1)</td>
<td>Beriberi</td>
<td>Neuropathy, cardiomyopathy, encephalopathy</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td></td>
<td>Angular stomatitis, dermatitis</td>
</tr>
<tr>
<td>Niacin</td>
<td>Pellagra</td>
<td>Dermatitis, dementia, diarrhea</td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td></td>
<td>Glossitis, neuropathy</td>
</tr>
<tr>
<td>Folate</td>
<td></td>
<td>Marocytic anemia</td>
</tr>
<tr>
<td>Cobalamin (B12)</td>
<td></td>
<td>Combined systems disease, anemia, dementia, spinal degenerat</td>
</tr>
</tbody>
</table>
Combined systems disease, anemia, dementia, spinal degeneration
Clinical situations in which vitamin deficiency syndromes occur

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor intake</td>
<td>Poverty, elderly, alcoholics, restrictive diets (eg vegan), parenteral nutrition</td>
</tr>
<tr>
<td>Malabsorption</td>
<td>Celiac disease, inflammatory bowel disease, short bowel, gastric bypass, elderly</td>
</tr>
<tr>
<td>Abnormal losses</td>
<td>Hemodialysis, chronic diarrhea</td>
</tr>
<tr>
<td>Abnormal metabolism</td>
<td>Genetic polymorphisms, alcoholism (increases folate metabolism)</td>
</tr>
<tr>
<td>Inadequate synthesis</td>
<td>Vitamin D (Northern climates, homebound, little exposed skin)</td>
</tr>
</tbody>
</table>

Recommended daily allowance (RDA) for vitamins

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dietary Reference Intake (DRI)*</th>
<th>Dietary Reference Intake (DRI)* in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men over age 18</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>900 mcg</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>5-15 mcg*</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>15 mg</td>
<td></td>
</tr>
<tr>
<td>K</td>
<td>120 mcg</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>90 mg</td>
<td></td>
</tr>
<tr>
<td>B1 (thiamine)</td>
<td>1.2 mg</td>
<td></td>
</tr>
<tr>
<td>B2 (riboflavin)</td>
<td>1.3 mg</td>
<td></td>
</tr>
<tr>
<td>Niacin</td>
<td>16 mg</td>
<td></td>
</tr>
<tr>
<td>B6 (pyridoxine)</td>
<td>1.3-1.7 mgΔ</td>
<td></td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 mcg</td>
<td></td>
</tr>
<tr>
<td>B12 (cobalamin)</td>
<td>2.4 mcg</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Women over age 18</strong></th>
<th>Dietary Reference Intake (DRI)* in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>700 mcg</td>
</tr>
<tr>
<td>D</td>
<td>5-15 mcg*</td>
</tr>
<tr>
<td>E</td>
<td>15 mg</td>
</tr>
<tr>
<td>K</td>
<td>90 mcg</td>
</tr>
<tr>
<td>C</td>
<td>75 mg</td>
</tr>
<tr>
<td>B1 (thiamine)</td>
<td>1.1 mg</td>
</tr>
</tbody>
</table>
### Relevant conversions:

Vitamin A is given in mcg as retinal activity equivalents. Conversion to beta-carotene is 12 mcg per retinol equivalent.

Vitamin D is given as cholecalciferol. Conversion is 1 mcg per 40 units vitamin D.

Vitamin E is given as alpha-tocopherol. Approximately 15 mg is 22 units natural vitamin E or 33 units synthetic vitamin E.

* DRI: this is the RDA for all vitamins except vitamin D and vitamin K; in those instances the DRI represents the Adequate Intake, since the RDA is not defined.

- Vitamin D: 5 mcg for age 19-50, 10 mcg for age 51-70, and 15 mcg over age 70.
- Δ Vitamin B6: 1.3 mg for age 19-50, 1.7 for age 51 and older.
- ◊ Vitamin B6: 1.3 mg for age 19-50, 1.5 for age 51 and older.


### Dietary reference intakes for fat-soluble vitamins

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Age group</th>
<th>RDA/AI</th>
<th>UL</th>
<th>Adverse effects of excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin A</td>
<td>Infants</td>
<td></td>
<td>Micrograms daily</td>
<td>Micrograms daily</td>
</tr>
<tr>
<td></td>
<td>0-6 months</td>
<td>400</td>
<td>600</td>
<td>Ataxia, alopecia, hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>7-12 months</td>
<td>500</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 to 3 years</td>
<td>300</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 to 8 years</td>
<td>400</td>
<td>900</td>
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</tr>
<tr>
<td></td>
<td>Males</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>9 to 13 years</td>
<td>600</td>
<td>1700</td>
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</tr>
<tr>
<td></td>
<td>14 to 18 years</td>
<td>900</td>
<td>2800</td>
<td></td>
</tr>
</tbody>
</table>
### Vitamin A

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Micrograms daily</th>
<th>1 mcg retinol activity equivalent = 3.3 unit vitamin A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
<td>900 3000</td>
</tr>
<tr>
<td>9 to 13 years</td>
<td>600 1700</td>
<td>Ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain; teratogenic</td>
</tr>
<tr>
<td>14 to 18 years</td>
<td>700 2800</td>
<td></td>
</tr>
<tr>
<td>≥19 years</td>
<td>700 3000</td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td></td>
<td>900 3000</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>750 2800</td>
<td></td>
</tr>
<tr>
<td>≥19 years</td>
<td>770 3000</td>
<td></td>
</tr>
<tr>
<td>Lactation</td>
<td></td>
<td>900 3000</td>
</tr>
<tr>
<td>&lt;18 years</td>
<td>1200 2800</td>
<td></td>
</tr>
<tr>
<td>≥19 years</td>
<td>1300 3000</td>
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</tbody>
</table>

### Vitamin D

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Micrograms daily</th>
<th>Micrograms daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 12 months</td>
<td>10 (400 IU)</td>
<td>0 to 6 months: 25 (1000 IU) 6 to 12 months: 37.5 (1500 IU)</td>
</tr>
<tr>
<td>Children and adolescents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 to 18 years</td>
<td>15 (600 IU)</td>
<td>1 to 3 years: 62.5 (2500 IU) 4 to 8 years: 75 (3000 IU) 9 to 18 years: 100 (4000 IU)</td>
</tr>
<tr>
<td>Males and females (including pregnancy and lactation)</td>
<td></td>
<td></td>
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<tr>
<td>19 to 50 years</td>
<td>15 (600 IU)</td>
<td>100 (4000 IU)</td>
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<tr>
<td>50 to 70 years</td>
<td>15</td>
<td>100</td>
</tr>
<tr>
<td>&gt;70 years</td>
<td>20 (800 IU)</td>
<td>100</td>
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</tbody>
</table>

### Vitamin E

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Milligrams daily</th>
<th>Milligrams daily</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>
hepatotoxicity, bone and muscle pain;
(alpha-tocopherol)
1 mg = 1.47 IU "natural source" vitamin E, or 2.2 IU synthetic vitamin E

<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
<th>Children</th>
<th>Males and females (including pregnancy)</th>
<th>Lactation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-6 months</td>
<td>1 to 3 years</td>
<td>9 to 13 years</td>
<td>≤18 years</td>
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<td></td>
<td>7-12 months</td>
<td>4 to 8 years</td>
<td>14 to 18 years</td>
<td>&gt;18 years</td>
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<td></td>
<td></td>
<td>&gt;18 years</td>
<td></td>
<td>&gt;19 years</td>
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<td>4</td>
<td>6</td>
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<td>60</td>
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</tr>
<tr>
<td>Vitamin K</td>
<td>Micrograms daily</td>
<td>Micrograms daily</td>
<td>Micrograms daily</td>
<td>Micrograms daily</td>
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</tr>
<tr>
<td>Infants</td>
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</tr>
<tr>
<td>0-6 months</td>
<td>2</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>7-12 months</td>
<td>2.5</td>
<td>55</td>
<td>75</td>
<td>120</td>
</tr>
<tr>
<td>Children</td>
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<tr>
<td>1 to 3 years</td>
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<tr>
<td>Males</td>
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<td>14 to 18 years</td>
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<tr>
<td>&gt;19 years</td>
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<td></td>
</tr>
<tr>
<td>Females</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>(including pregnancy and lactation)</td>
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</tr>
</tbody>
</table>

Increased risk of bleeding; possibly increased risk of necrotizing enterocolitis in infants

No adverse effects associated with vitamin K consumption from food supplements have been reported, however data are limited.
Increased risk of bleeding; possibly no adverse effects associated with vitamin K consumption from food or supplements have been reported.
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Vitamin A (RAE)</th>
<th>AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 to 13 years</td>
<td>60</td>
<td>ND</td>
</tr>
<tr>
<td>14 to 18 years</td>
<td>75</td>
<td>ND</td>
</tr>
<tr>
<td>&gt;19 years</td>
<td>90</td>
<td>ND</td>
</tr>
</tbody>
</table>

Vitamin A doses given as retinol activity equivalents (RAE). 1 RAE = 1 mcg retinol, 12 mcg beta-carotene, 14 mcg alpha-carotene, or 24 mcg beta-cryptoxanthin.

RDA: recommended dietary allowance.

AI: adequate intake.
