Vitamin intake and disease prevention

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All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Apr 2024.**
This topic last updated: **Nov 08, 2023.**

INTRODUCTION

Vitamins are chemically unrelated families of organic compounds that are essential in small amounts for normal metabolism. Because most vitamins cannot be synthesized by humans, they need to be ingested in the diet to maintain health and prevent disease. The exceptions to this are pre-vitamin D_3, which is synthesized in the skin following ultraviolet (UV) exposure, and vitamins K2 and B12, which can be synthesized by colonic microbes. These should be distinguished from minerals (such as calcium and iron), some of which are also essential micronutrients.

Pregnancy, lactation, alcohol consumption, and chronic use of certain medications increase certain vitamin requirements. The value of vitamin supplementation in the prevention or reversal of many chronic diseases has been disproven in most cases and has proven harmful in others. Randomized trials often fail to confirm the associations seen in observational studies. Additionally, methodological flaws, including lack of standardization of baseline vitamin status and varying doses, often pharmacologic, may contribute to inconsistent findings [1,2].

The evidence for enhancing vitamin intake through diet or supplementation to prevent chronic disease is reviewed here. Overviews of individual vitamins, dietary minerals, and dietary supplements are also discussed separately:

- (See "Overview of water-soluble vitamins".)
- (See "Overview of vitamin A".)
- (See "Overview of vitamin D".)
- (See "Overview of dietary trace elements".)

- (See "Overview of vitamin E".)

VITAMIN DEFICIENCY AND DEFINITIONS OF ADEQUATE INTAKE

The concept of vitamin deficiency has evolved, from the recognition of obvious vitamin deficiency syndromes such as scurvy, pellagra, beriberi, to the subtle effects of suboptimal vitamin intake on chronic diseases. (See "Micronutrient deficiencies associated with protein-energy malnutrition in children".)

Gross vitamin deficiency may be recognized by obvious clinical syndromes, which are still seen in areas of the world with very poor diets (table 1). In resource-rich societies, they also occur in several particular populations, including some older adults; vegans; new immigrants who may arrive with preexisting deficiencies [3,4]; those experiencing significant poverty; patients with alcohol use disorder, malabsorption disorders, limited sun exposure, history of bariatric surgery, or inborn errors of metabolism; and those undergoing hemodialysis or receiving parenteral nutrition (table 2). However, the levels of numerous vitamins are impacted by underlying disease, and low levels may not reflect actual deficiency.

There are several ways of defining optimal vitamin intake. Dietary reference intakes (DRIs) represent four concepts:

- Recommended Dietary Allowance (RDA)
- Adequate Intake (AI)
- Estimated Average Requirement (EAR)
- Tolerable Upper Intake Level (UL)

In the United States, DRIs are established by the National Academy of Sciences, National Research Council, and the Institute of Medicine (IOM) (table 3 and table 4 and table 5 and table 6). For clinical purposes, we use the RDA, which is the recommended 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 (including vitamin supplementation in infants <12 months and for vitamin K) (table 3). However, AI levels may not be adequate for all people, since they are largely based upon observational studies of intake among healthy individuals.

Testing — Although measurement of serum levels of several vitamins is widely available, testing for deficiencies is usually unwarranted:

- For some vitamins, there is insufficient information about the optimum serum levels of vitamins, making it difficult to interpret the results and diagnose subtle deficiency states.

- There is insufficient evidence that vitamin supplementation can prevent disease in most healthy adults with low serum levels of vitamins (apart from those individuals with specific diets or medical conditions).

- The levels of numerous vitamins are impacted by underlying disease, and low levels may not reflect actual deficiency.

However, testing remains appropriate in certain clinical situations where deficiencies are suspected or are part of the clinical evaluation (eg, measuring 25-hydroxyvitamin D in patients with osteoporosis and vitamin B12 in patients with cognitive decline of unknown etiology). (See "Evaluation of cognitive impairment and dementia", section on 'Laboratory testing' and "Evaluation and treatment of premenopausal osteoporosis", section on 'Initial evaluation'.)

Additional information about genetic polymorphisms, which increase requirements for specific vitamins, is likely to become available. This appears to be the case for certain genes, such as those controlling the metabolism of folate and vitamin D. However, there is insufficient understanding of individual risk to warrant routine testing for polymorphisms. (See "Pathogenesis of osteoporosis", section on 'Genetics'.)

FOLIC ACID

- Folate is the natural form of the vitamin found in food and is present in green, leafy vegetables, fruits, cereals, grains, nuts, and meats.

- Folic acid is the synthetic form of the vitamin that is included in supplements and food fortification and has many of the same biologic effects as folate, but it is more bioavailable and therefore more effective dose for dose [5].

Some evidence suggests that the metabolism of folic acid differs from folate and may have toxicities under certain circumstances [6]. Gross deficiency of folate leads to megaloblastic anemia. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Diagnostic evaluation'.)

Folic acid has been studied for prevention of many disease states. However, the only well-established benefit of folic acid supplementation is the prevention of neural tube defects. In the United States, concern over the risk for neural tube defects led to nationwide folate fortification of all enriched cereal grains beginning in 1998.

Neural tube defects — Folic acid supplementation reduces the risk of neural tube defects, probably because folate is required for normal cell division. This has been shown in multiple observational studies and confirmed by randomized trials [7-11]. Females of childbearing potential are recommended to consume 400 mcg of folic acid daily, with higher intake recommended for those with certain risk factors (table 7). This is discussed in detail elsewhere. (See "Preconception and prenatal folic acid supplementation", section on 'Folic acid supplementation for preventing NTDs'.)

Cancer — Folate deficiency may contribute to aberrant deoxyribonucleic acid (DNA) synthesis and carcinogenesis by decreasing methionine availability and interfering with normal DNA methylation. Observational evidence suggests that sufficient folate intake might be associated with prevention of cancers in certain populations at increased risk [12-15], although randomized trials have not confirmed any benefits of folic acid supplementation and have also raised the possibility of harm [16-19]. (See "Causes and pathophysiology of vitamin B12 and folate deficiencies".)

In a 2013 meta-analysis of randomized trials (including three trials and over 2600 patients with colorectal adenoma, and 10 trials and 47,000 subjects evaluating folic acid for the prevention of cardiovascular disease [CVD]), there was no difference in overall cancer incidence among those assigned to folic acid compared with placebo over 5.2 years of treatment [20]. In addition, there was no difference in the incidence of specific cancers between the groups. Among the included trials, the doses of folic acid ranged from 0.5 to 5 mg daily, which is higher than the RDA for the healthy adult. An additional limitation was the short intervention duration which may be insufficient to identify any long-term benefits or harms. Finally, the included trials did not address underlying nutritional status and other preventive measures.

Cardiovascular disease — High levels of homocysteine are associated with an increased risk of CVD [21], and supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels. However, there is no evidence of efficacy of folate supplementation in the prevention of CVD. This is discussed elsewhere. (See "Overview of homocysteine", section on 'Disease associations'.)

Other — Elevated homocysteine levels have been associated with osteoporosis and dementia. It is not known whether these associations are causal or represent overall dietary quality, and there is limited high-quality evidence that lowering homocysteine levels with folic acid supplementation is effective in preventing these conditions. (See "Overview of homocysteine", section on 'Disease associations' and "Risk factors for cognitive decline and dementia", section on 'Homocysteine' and "Prevention of dementia", section on 'Vitamins B6, B12, and folate' and "Overview of the management of low bone mass and osteoporosis in postmenopausal women", section on 'Therapies not recommended'.)

In addition, excess folate intake (approximately twice the recommended dose) has been associated with peripheral neuropathy, despite normal serum levels of vitamin B12, in older individuals who have a common polymorphism in the transcobalamin vitamin B12 transporter gene [22].

VITAMIN D

There is controversy over whether subclinical vitamin D deficiency or insufficiency contribute to the development of osteoporosis, falls, and fractures in older adults. The concept of vitamin D “insufficiency” resulted from associations made in observational studies, but randomized trials have not demonstrated benefit of supplementation in patients with poor vitamin D status (defined as <10 or <20 ng/mL [<25 or <50 nmol/L]).

Serum 25-hydroxyvitamin D should be measured in patients who are at risk for inadequate serum vitamin D concentrations, including institutionalized individuals, patients being evaluated for osteoporosis, and patients with malabsorption (eg, Crohn disease and celiac disease). The evaluation and supplementation of vitamin D in patients with vitamin D deficient states and in patients with osteoporosis are discussed in detail elsewhere. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment" and "Calcium and vitamin D supplementation in osteoporosis" and "Vitamin D insufficiency and deficiency in children and adolescents" and "Vitamin D and extraskeletal health".)

The intake at which the dose of vitamin D becomes toxic is not clear. The Institute of Medicine (IOM) has defined the upper limit for vitamin D as 4000 units daily for healthy adults [23]. This is also the upper limit for pregnant and lactating individuals. It is important to ask patients about additional dietary supplements (some of which contain vitamin D) before prescribing supplemental vitamin D [24]. (See "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment", section on 'Vitamin D replacement'.)

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 "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment", section on 'Clinical manifestations' and "Calcium and vitamin D supplementation in osteoporosis".)

Falls — There are several meta-analyses of randomized trials showing a reduction in risk of falls following vitamin D supplementation, particularly when the baseline vitamin D status is poor

[25-29]. This is reviewed in detail elsewhere. (See "Falls: Prevention in community-dwelling older persons", section on 'Vitamin D supplementation' and "Vitamin D and extraskeletal health", section on 'Falls'.)

Cancer — While there are biologic reasons why vitamin D might protect against cancer, evidence for this effect in humans is mixed, and expert groups do not recommend vitamin D supplements for the specific purpose of cancer prevention [30]. This is reviewed in detail elsewhere. (See "Vitamin D and extraskeletal health", section on 'Cancer'.)

Mortality — Studies evaluating the relationship between vitamin D levels and mortality have demonstrated conflicting results. The evidence regarding vitamin D and mortality is discussed separately. (See "Vitamin D and extraskeletal health", section on 'Mortality'.)

Other — In addition to its role in calcium and bone homeostasis, vitamin D potentially regulates many cellular and immune functions. Vitamin D deficiency has been implicated as a risk factor for many diseases, although a causal relationship between poor vitamin D status and major diseases, including infections, autoimmune disorders, cardiovascular, and metabolic diseases, has not been established [31]. For example, despite observational studies identifying an association between low vitamin D levels and unfavorable coronavirus disease 2019 (COVID-19) outcomes, randomized trials have failed to demonstrate the efficacy of vitamin D supplementation in treating COVID-19 [32]. The role of vitamin D in extraskeletal health is reviewed in detail separately. (See "Vitamin D and extraskeletal health".)

ANTIOXIDANTS

Nutritional antioxidants include those consumed from both dietary and supplemental sources. The common dietary antioxidants are vitamins A (including some carotenoids with little vitamin A activity), C, and E. The bioavailability of nutritional antioxidants may be impacted by the simultaneous consumption of other foods and drinks. Dietary antioxidants most often refer to those found in fruits, vegetables, and other foods, such as nuts, oils, seeds, and wine.

Potential mechanisms of benefit — It is hypothesized that antioxidants can prevent cancer and cardiovascular disease (CVD) by augmenting the body's ability to dispose of toxic free radicals, thereby retarding oxidative damage [33]. Inflammation and oxidative stress are critical to the initiation and progression of atherosclerosis; oxidation of proteins and lipid peroxidation of membrane polyunsaturated fatty acids in lipoproteins can facilitate the development of atherosclerotic lesions (figure 1).

Ingestion of nutritional antioxidants may retard atherosclerosis through several different mechanisms (figure 2) [34-36]. Antioxidants provide cellular protection by inducing enzyme-catalyzed processes that alter the steady state levels of crucial regulatory elements through signal transduction pathways, especially the nuclear factor erythroid 2 (Nrf2) transcription factor and electrophile response element (EpRE) to which Nrf2 binds. Our understanding of how these dietary antioxidants and possibly supplemental antioxidants effect protection against oxidative damage continues to evolve [37].

Dietary sources — In observational studies, diets high in vegetables and fruits that are rich in antioxidants are associated with a reduced risk of cancer and CVD [38,39]. However, the association may be due to non-vitamin antioxidants, other compounds such as flavonoids, the substitution of dietary meat and fat with vegetables and fruits, or the other components of healthy lifestyles seen in people who consume this dietary pattern.

The empirical dietary inflammatory pattern (EDIP), a food-based dietary index, has been developed to evaluate the inflammatory potential of diets, considering consumption of foods rich in antioxidants as well as foods with high proinflammatory potential; a higher score reflects a proinflammatory dietary pattern [40]. In an observational analysis, a higher EDIP was associated with elevated circulating inflammatory markers including lower adiponectin, tumor necrosis factor (TNF) alpha-R2, and high-sensitivity C-reactive protein (hs-CRP) [41]. In a large observational study including over five million person-years of follow-up, a higher EDIP was associated with increased risk of incident CVD, coronary heart disease, and stroke (hazard ratio [HR] 1.38, 95% CI 1.31-1.46; HR 1.46, 95% CI 1.36-1.56; HR 1.28, 95% CI 1.17-1.39) [42]. These benefits were not identified in randomized trials.

No role for supplements — We do not advise the use of antioxidant supplements strictly to prevent the development of atherosclerotic CVD or cancer. This is consistent with the recommendations from the US Preventive Services Task Force (USPSTF), which found insufficient evidence to recommend for or against supplements of vitamin A, vitamin C, or antioxidant combination supplements for the prevention of atherosclerotic CVD and recommends **against** the use of beta-carotene or vitamin E supplements for this purpose [30]

Randomized trials evaluating antioxidant supplements have not found a reduction in the risk of cancer [43]. Further, supplementation with vitamin E, vitamin C, and beta-carotene (provitamin A carotenoid) has not been shown to be useful for primary or secondary prevention of CVD whether given alone or in combination [44-48].

Vitamin A and the carotenoids — Vitamin A consists of preformed vitamin A (retinol) and the provitamin A carotenoids (alpha- and beta-carotenes) that can be converted into vitamin A.

Retinol is only found in animal products (eg, liver, milk, egg yolk, butter) and supplements. The provitamin A carotenoids are ubiquitous in yellow and orange fruits and vegetables as well as leafy green vegetables. In addition to antioxidant properties, retinol can induce cellular differentiation. (See "Overview of vitamin A", section on 'Cellular differentiation'.)

Most diets in resource-rich countries contain adequate amounts of retinol and carotenoids. Vegetarians, including vegans, do not need to take vitamin A supplements if they eat an adequate variety of carotenoid containing vegetables. While vitamin A supplementation for children ages 6 through 59 months in resource-limited countries is recommended to prevent blindness and reduce mortality, dietary intake of vitamin A in other countries is generally adequate [49,50]. Thus, in countries with adequate resources, routine vitamin A or beta-carotene supplementation is not warranted given lack of proven efficacy and the possibility of harm. A detailed discussion of indications for vitamin A supplementation can be found elsewhere. (See "Overview of vitamin A", section on 'Requirements'.)

Cancer — Trials evaluating vitamin A or carotenoid supplementation have reported no benefit or an increased risk of cancer [51-61]. As examples:

- Two large, randomized trials assessed the effect of beta-carotene supplementation on the risk of lung cancer among males at increased risk because of smoking or asbestos exposure [51,52]. In both trials, there was an increased lung cancer risk among men who received the supplements; the excess risk resolved over time once supplements were stopped [53]. (See "Chemoprevention of lung cancer", section on 'Investigative strategies'.)

- In the ATBC Cancer Prevention Study, there was an increase in both prostate cancer incidence and mortality among participants randomly assigned to receive beta-carotene [62]. The excess risk resolved over time (four to six years) after supplements were stopped [53].

- In pooled analysis from a USPSTF systematic review of 84 studies, beta carotene (with or without vitamin A) was associated with an increased risk of lung cancer (odds ratio [OR] 1.20, 95% CI 1.01-1.42) among persons at high risk of lung cancer [47].

The increase in risk of cancer in randomized trials of beta-carotene as described above (albeit in high-risk individuals) has dampened enthusiasm for further clinical trials of antioxidants in cancer prevention.

Cardiovascular disease — Randomized trials of vitamin A and beta-carotene have shown no benefit for the primary or secondary prevention of coronary heart disease (CHD), and further, one trial, as well as a USPSTF systematic review, suggested potential harm with regard to cardiovascular mortality [47,63]. This is discussed elsewhere. (See "Prevention of cardiovascular disease events in those with established disease (secondary prevention) or at very high risk", section on 'Therapies with uncertain or no benefit' and "Overview of vitamin E", section on 'Potential risks'.)

Immunity — Vitamin A improves immunity in children living in resource-limited countries where dietary intake is inadequate and life-threatening infectious diseases are common. In a meta-analysis including 12 randomized trials, vitamin A supplementation in children with measles in resource-limited settings reduced mortality in both hospitalized and non-hospitalized patients [64]. (See "Measles: Clinical manifestations, diagnosis, treatment, and prevention", section on 'Vitamin A'.)

The World Health Organization (WHO) recommends community-based vitamin A supplementation for children in resource-limited countries even in the absence of signs and symptoms of deficiency [65]. (See "Overview of vitamin A", section on 'Special populations'.)

Fractures — Consistent evidence from observational studies suggests that higher vitamin A intake (specifically retinol) is a risk factor for osteopenia and fractures [66-68]. As an example, over 72,000 postmenopausal females ages 34 to 77 years were followed for 18 years in the Nurses' Health Study [67]. Those in the highest quintile of total vitamin A intake had an increased risk for hip fracture compared with those in the lowest quintile (relative risk [RR] 1.48, 95% CI 1.05-2.07). Thus, patients should be cautioned against diets high in retinol, especially if they have other risk factors for osteopenia, and should avoid vitamin A supplements if their dietary intake is high. (See "Drugs that affect bone metabolism", section on 'Vitamin A and synthetic retinoids'.)

Congenital anomalies — Supplements with preformed vitamin A in doses >10,000 international units taken in the first trimester of pregnancy have been shown to increase the risk of congenital anomalies [69]. (See "Overview of vitamin A", section on 'Teratogenic effects'.)

Cataracts and macular degeneration — In randomized trials, there was no benefit of vitamin A or carotenoid supplementation in the primary prevention of cataracts or macular degeneration. (See "Cataract in adults", section on 'Prevention' and "Age-related macular degeneration", section on 'Limited role for antioxidant vitamins'.)

Vitamin C — Vitamin C (ascorbic acid) is a water-soluble vitamin and is found in particularly high amounts in citrus fruits, peppers, tomatoes, and leafy greens. Evidence does not support the use of vitamin C supplementation for chronic disease prevention, including cancer or primary or secondary prevention of CHD.

Cancer — Large randomized trials have found no reduction in the incidence of cancers among patients given vitamin C supplementation [70]. As examples:

- In the Physicians' Health Study II, over 14,000 males age ≥50 were randomly assigned to receive vitamin C 500 mg daily or placebo [71]. After eight years of treatment, there was no difference in the incidence of cancers between groups, and during an additional three years of post-trial follow-up, there was no difference in the risk of all cancers and prostate cancers between the two groups [72].

- In an analysis of the Women's Antioxidant Cardiovascular Study including almost 8000 females, vitamin C 500 mg daily for 9.4 years had no effect on the incidence of cancers [56].

Cardiovascular disease — Randomized trials have shown no benefit of vitamin C for primary or secondary prevention of CHD. (See "Overview of possible risk factors for cardiovascular disease", section on 'Vitamins, antioxidants and homocysteine'.)

Infection — Vitamin C may have a minor role in reducing the duration of cold symptoms in adults, although the clinical importance of this is likely small [73]. Further, there is no evidence that regular vitamin C supplementation reduces the incidence of the common cold. (See "The common cold in adults: Treatment and prevention".)

Kidney stones — Vitamin C increases urinary oxalate excretion and may increase the risk of kidney stones. This is discussed elsewhere. (See "Kidney stones in adults: Epidemiology and risk factors".)

Cataracts and macular degeneration — In randomized trials, there was no benefit of vitamin C supplementation in the primary prevention of cataracts or macular degeneration [74]. (See "Cataract in adults", section on 'Prevention' and "Age-related macular degeneration", section on 'Limited role for antioxidant vitamins'.)

Vitamin E — There are a number of biologically active vitamin E compounds, including alpha-, beta-, gamma-, and delta- tocopherol. Vitamin E is present in vegetable oils such as wheat germ, sunflower, safflower, and lesser amounts in corn and soybean oils. Nuts, especially almonds, hazelnuts, peanuts, and seeds (eg, sunflower) are good sources of vitamin E. Additionally, vitamin E is found in green leafy vegetables such as broccoli and spinach. (See "Overview of vitamin E", section on 'Sources' and "Overview of vitamin E", section on 'Chemistry and nomenclature'.)

Evidence does not support a role for vitamin E supplementation in the prevention or treatment of cancers, CVD, dementia, and infection. Additionally, the best available evidence suggests that high-dose vitamin E (≥400 units daily) might increase all-cause mortality [75]. In particular, individuals taking anticoagulants should be advised against high doses of vitamin E because of the synergistic action of vitamin E with these drugs. Vitamin E is discussed in detail elsewhere. (See "Overview of vitamin E".)

Cancer — Observational studies have found variable effects of vitamin E on certain cancers, particularly within subgroups such as people who smoke [57-59,76-78], but most randomized trials do not support a protective effect [56,61,71,79-81].

As an example, in the Women's Health Study, a randomized trial that followed almost 40,000 healthy females age ≥45 for a mean of 10.1 years, supplementation with 600 units of natural-source vitamin E on alternate days had no effect on the incidence of all cancers, breast cancer, lung cancer, colon cancer, or cancer mortality compared with placebo [79].

In addition, randomized trials of vitamin E for prevention of prostate cancer have found conflicting results (see "Chemoprevention strategies in prostate cancer", section on 'Vitamin E'):

- In the ATBC Cancer Prevention Study, there was a 16 percent decrease in prostate cancer mortality over 18 years of follow-up (RR 0.84, 95% CI 0.70-0.99) among male smokers randomly assigned to receive 50 mg (75 units) of alpha-tocopherol for five to eight years, compared with placebo [82].

- The SELECT trial followed over 35,000 males (ages ≥50 for African American participants and ages ≥55 for other participants) for a median of seven years [83]. Compared with placebo, vitamin E supplementation (400 units daily) was associated with an increased risk of prostate cancer (HR 1.17, 99% CI 1.004-1.36).

Cardiovascular disease — Nearly all randomized trials of vitamin E have shown no benefit for the primary or secondary prevention of CHD [63]. Additionally, vitamin E supplementation may increase the risk of heart failure [80]. (See "Overview of possible risk factors for cardiovascular disease", section on 'Vitamins, antioxidants and homocysteine'.)

Additionally, randomized trials have not found overall benefit of vitamin E supplementation in stroke prevention. In a meta-analysis including nine randomized trials, vitamin E supplementation had no effect on risk of total stroke [84]. Findings were similar for patients with and without established CVD. Vitamin E supplementation was, however, associated with an increased risk of hemorrhagic stroke although a decreased risk of ischemic stroke (RR 1.22, 95% CI 1.00-1.48; RR 0.90, 95% CI 0.82-0.99, respectively).

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 [85-87], randomized trials have found no benefit of vitamin E supplementation for the prevention of dementia [88,89]. (See "Prevention of dementia", section on 'Antioxidant vitamins' and "Treatment of Alzheimer disease", section on 'Antioxidants'.)

Infection — Several studies have reported that supplementation with vitamin E improves the immune response [90,91]. Such an effect is of particular interest in older adults, in whom an age-related decline in immune response may increase the risk of infections and related complications. However, randomized trials examining vitamin E to prevent infections in older adults have not found clinical benefits [92-94]. Large trials found no reduction in the incidence of respiratory infections among institutionalized [92,93] and noninstitutionalized [94] older adult patients receiving daily vitamin E supplements. Furthermore, in a trial of noninstitutionalized older adults experiencing a respiratory infection, those who received vitamin E (200 mg daily) experienced more symptoms, a longer total illness duration (19 versus 14 days), and a higher frequency of fever and activity restriction [94].

Venous thromboembolism — High doses of vitamin E may interfere with vitamin K and affect coagulation. As an example, in a secondary analysis from the Women's Health Study, females randomly assigned to receive 600 units vitamin E every other day had a lower risk of venous thromboembolism than those receiving placebo (HR 0.79, 95% CI 0.66-0.94) [95]. This effect needs to be confirmed in other randomized trials before vitamin E can be recommended for prevention of venous thromboembolism.

Cataracts and macular degeneration — Randomized trials have found no benefit of vitamin E supplementation in the prevention of cataracts or macular degeneration [74,96]. (See "Cataract in adults", section on 'Prevention' and "Age-related macular degeneration", section on 'Limited role for antioxidant vitamins'.)

All-cause mortality — There is no evidence of a mortality effect of vitamin E supplementation.

- A meta-analysis of randomized trials of vitamin E supplementation examined the effects of supplementation on all-cause mortality [75]. Although there was no overall effect on mortality across all trials, mortality was increased among patients who received high-dose vitamin E supplementation (≥400 units daily), with an increase in mortality of 39 per 10,000 persons, 95% CI 3-74 per 10,000 persons. There also appeared to be a dose-response relationship, with patients treated with low-dose supplementation experiencing a decrease in mortality. However, trials evaluating these doses were often performed in malnourished populations or used with supplements in combination with vitamin E.

Further, several trials of high-dose supplementation were performed 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, another meta-analysis that did not stratify trials by dose found no overall effect of vitamin E supplementation on all-cause mortality [63].

VITAMIN B2 (RIBOFLAVIN)

Vitamin B2 is found in many commonly consumed foods, including milk, meat, eggs, cereal, and green leafy vegetables. This may explain why overt riboflavin deficiency is rare.

There is no strong evidence that supplemental vitamin B2 is helpful in healthy people eating a balanced diet, although B2 supplementation may have a role in management in adults with episodic migraines. This is discussed elsewhere. (See "Preventive treatment of episodic migraine in adults", section on 'Other agents'.)

VITAMIN B6 (PYRIDOXINE)

Vitamin B6 is found in bananas, nuts, and many common vegetables such as potatoes, green beans, cauliflower, and carrots. Vitamin B6 is thought to reduce the risk of cardiovascular disease (CVD) and cancer. However, it has been difficult to distinguish the effects of vitamin B6 from that of other vitamins and of other substances in fruits and vegetables [97].

High levels of homocysteine are associated with an increased risk of CVD, and supplementation with folic acid, vitamin B6, and vitamin B12 can lower homocysteine levels. However, randomized trials of supplementation for secondary prevention do not support the hypothesis that these vitamins prevent CVD [98-102]. (See "Overview of homocysteine".)

Higher levels of vitamin B6 and their metabolites are associated with a lower risk of cancer. However, randomized trials of B6 supplementation have not demonstrated a benefit in cancer risk reduction [103].

VITAMIN B12 (COBALAMIN)

Suboptimal vitamin B12 levels are most commonly caused by poor absorption or inadequate intake of vitamin B12-containing food sources (eg, liver, milk, fish, meat). Malabsorption of cobalamin is primarily the result of inability to release cobalamin from dietary proteins, especially in the presence of autoimmune antibodies against intrinsic factor or reduced gastric acid secretion. Patients treated with metformin also have decreased vitamin B12 absorption (see "Metformin in the treatment of adults with type 2 diabetes mellitus", section on 'Vitamin B12 deficiency'). In older adults, gastric atrophy and hypochlorhydria result in reduced gastric acid and inefficient vitamin B12 absorption. Low levels of vitamin B12 can also be seen among people following a vegan diet. (See 'Special diets' below and "Causes and pathophysiology of vitamin B12 and folate deficiencies", section on 'Causes of vitamin B12 deficiency'.)

Vitamin B12 deficiency is associated with neuropsychiatric manifestations and megaloblastic anemia. This is discussed in detail elsewhere. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency", section on 'Clinical presentation'.)

Measuring vitamin B12 levels may be indicated in individuals at increased risk for poor vitamin B12 intake, including vegans, people taking metformin, those with alcohol use disorder, and people with little dietary variation or poor-quality diets (such as some older adults and people experiencing poverty) (algorithm 1). In the absence of a strong evidence base about the impact of supplementation on clinical outcomes, we recommend using clinical judgment and shared decision-making to determine when to test asymptomatic but at-risk people for vitamin B12 deficiency. Similarly, there is not yet an evidence base to recommend routine supplementation of at-risk people. However, vitamin B12 supplementation is well-tolerated without significant adverse effects, and we suggest it for some at-risk patients, such as those adhering to a vegan diet (see 'Special diets' below) [104,105].

Because impaired vitamin B12 absorption is so common among older adults, consumption of foods fortified with vitamin B12 has been advised. Taking a multivitamin is a reasonable alternative [106,107].

The evaluation and treatment of B12 deficiency is reviewed in detail elsewhere (algorithm 2). (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency" and "Treatment of vitamin B12 and folate deficiencies".)

MULTIVITAMINS

Most generic and brand-name multivitamins contain 50 to 150 percent of the Recommended Dietary Allowance (RDA) for all vitamins, including folic acid and vitamins A, C, D, E, B2, B6, and B12. However, there are several variations of multivitamins, such as B vitamins alone, multivitamins with minerals, and multivitamins for specific groups (eg, females, males, younger and older populations). The proposed rationale for taking a daily multivitamin for adults includes known or potential effectiveness for some of the component vitamins, relative safety in low doses, low cost (one multivitamin per day can cost as little as USD $15 to $35 per year in the United States, but can also be much more expensive), and efficiency of taking one pill rather than multiple vitamin pills.

Many multivitamins contain minerals as well, but the doses of minerals in these supplements (such as calcium and iron) are well below one daily value (DV). DVs are reference values that provide recommended dietary nutrient intakes that appear on package labels. Toxicities of individual minerals are discussed elsewhere. (See "Overview of dietary trace elements".)

Multivitamin supplementation should be considered for patients at risk for vitamin deficiency, such as those with alcohol use disorder, poor-quality diets with low fruit and vegetable intake, malabsorption, a vegan diet, a history of bariatric surgery, or some inborn errors of metabolism, as well as those being treated with hemodialysis or parenteral nutrition. In addition, in patients with a specific vitamin deficiency, a multivitamin may be a reasonable choice over supplementation with individual vitamins if a multivitamin is less costly and the formulation contains an appropriate dose. (See "Management of moderate and severe alcohol withdrawal syndromes", section on 'Management' and "Bariatric surgery: Postoperative nutritional management", section on 'Micronutrient management' and "Hyporesponse to erythropoiesis-stimulating agents (ESAs) in chronic kidney disease", section on 'Our approach to ESA hyporesponsiveness'.)

Efficacy — It has not been established that multivitamin and mineral supplements provide added benefit to a balanced, healthful diet for most individuals [108].

- In a 2021 evidence review for the US Preventive Services Task Force (USPSTF) including 84 trials, vitamin and mineral supplementation was associated with little or no benefit in preventing cancer, cardiovascular disease (CVD), or death, with the exception of a small benefit for cancer incidence with multivitamin use [47].

- In a trial conducted among 21,442 older adults in the United States, a daily multivitamin and cocoa extract supplement did not reduce the incidence of invasive cancer compared with placebo (hazard ratio [HR] 0.97, 95% CI 0.86-1.09) [48].

Consistent with the USPSTF and the US National Institutes of Health (NIH) consensus statement, in otherwise healthy people who have adequate dietary intake and no risk factors for inadequate vitamin status as discussed above, we suggest not taking multivitamin supplementation for primary prevention of chronic diseases because of insufficient evidence of benefit [30,109]. However, many patients wish to take multivitamins based on their own belief systems; we advise that clinicians not struggle against that practice as long as there is no absolute contraindication for an individual patient. Other experts disagree and would recommend more strongly against such supplements [110].

Safety — In the United States, the federal government does not regulate food supplements (vitamins, minerals, and herbs) to assure safety and efficacy [111]. Multivitamins are sold in a variety of combinations and doses, although manufacturers are required to list contents in a standard way, making it easier for consumers to compare brands.

Individual vitamin doses in multivitamins are safe for most adults. As examples, the dose of vitamin E is well below the levels reported to cause an increase in overall mortality, and the dose of beta-carotene is well below levels associated with lung cancer. The dose of folic acid is also lower than that found to potentially increase cancer risk.

However, there are potential risks of harm with vitamin supplementation. In a 2021 evidence review for the USPSTF including trials of multicomponent multivitamins, although adverse effects were rare, some supplements were associated with higher risk of serious harms (hip fracture [vitamin A], hemorrhagic stroke [vitamin E], and kidney stones [vitamin C, calcium]) [47]. Further, some formulations of vitamins sold over the counter may contain several times the RDA of vitamin B12 and should be avoided.

In addition, some individuals may be harmed by even ordinary doses of vitamin A. As an example, 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 United States. People at increased risk of osteopenia, or with relatively high dietary intake of vitamin A, should not take additional supplements containing vitamin A. Additionally, vitamin A is teratogenic at doses as low as 10,000 units daily of supplementation [69]. Although manufacturers have been reducing the amount of vitamin A in multivitamins, supplementation, even at less than 100 percent of the RDA, does not seem prudent in people who are otherwise at increased risk. (See 'Fractures' above and 'Toxicity at high doses' below.)

TOXICITY AT HIGH DOSES

Potentially toxic levels of individual 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 high. The Institute of Medicine (IOM) and the United States Office of Dietary Supplements has suggested Tolerable Upper Intake Levels (ULs) for specific vitamins, which is the highest daily dose that is unlikely to cause adverse health effects in the general population (table 5 and table 6).

Water-soluble vitamins (folate, vitamin C, B vitamins) can generally be tolerated at high doses, with toxicity occurring only at doses thousands of times the Recommended Dietary Allowance (RDA). A possible exception is the risk of kidney stones, which may be increased after doses of vitamin C that are 10 to 25 times the RDA.

Fat-soluble vitamins (vitamins A, D, E, K) are generally more toxic than water-soluble vitamins. Vitamin D may cause hypercalcemia at doses as low as 4000 units daily (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 daily of supplemental vitamin A) [69]. Beta-carotene appears to increase the risk of lung cancer in adults who are at high risk because of smoking or asbestos exposure. As discussed above, there are concerns that vitamin E supplementation above 400 units daily may be associated with increased all-cause mortality. (See 'Cancer' above and 'All-cause mortality' above.)

SPECIAL DIETS

People on restricted or special diets may have 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 foods is the main cause of low vitamin B12 levels; in older adults, malabsorption of vitamin B12 from foods is the most common cause [112]. The lowest intakes of vitamin B12 are seen in those who eat no animal products, and vitamin B12 intake increases with increasing intake of animal source foods [113]. (See "Treatment of vitamin B12 and folate deficiencies".)

People who consume a vegan diet (ie, a diet that excludes all animal products, including meat, eggs, milk, and milk products) should take a vitamin B12 supplement (at the RDA of 2.4 micrograms daily). They are also at risk for inadequate vitamin D status and should consider a supplement, particularly during winter months [114].

Lacto-ovo-vegetarians (ie, those who exclude meat, but consume eggs, milk, and milk products) and lacto-vegetarians (ie, those who exclude meat and eggs, but consume milk and milk products) should also consider supplementation with vitamin B12.

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. By 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-hydroxyvitamin D levels) based on the expected nutrient deficiencies in the diet.

RECOMMENDATIONS OF OTHERS

The US Preventive Services Task Force (USPSTF) clinical practice guidelines provide several recommendations for vitamin supplementation in adult populations:

- Vitamin, calcium, or combined supplementation for the primary prevention of fractures in community-dwelling adults: Preventive medication
- Vitamin, mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer: Preventive medication
- Folic acid for the prevention of neural tube defects: Preventive medication

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Vitamin deficiencies" and "Society guideline links: Healthy diet in adults".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5^{th} to 6^{th} grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10^{th} to 12^{th} grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to provide these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Vitamin D deficiency (The Basics)" and "Patient education: Vitamin B12 deficiency and folate deficiency (The Basics)" and "Patient education: Vitamin supplements (The Basics)")

- Beyond the Basics topic (see "Patient education: Calcium and vitamin D for bone health (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions of adequate intake –** There are several ways of defining optimal vitamin intake. Dietary reference intakes (DRIs) represent four concepts: Recommended Dietary Allowance (RDA), Adequate Intake (AI), Estimated Average Requirement (EAR), and Tolerable Upper Intake Level (UL) (table 3 and table 4 and table 5 and table 6). We use the RDA, which is the recommended 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. (See 'Vitamin deficiency and definitions of adequate intake' above.)

- **Testing for vitamin deficiencies –** Although measurement of serum levels of several vitamins is widely available, testing for deficiencies is usually unwarranted. Testing remains appropriate in certain clinical situations where deficiencies are suspected or are part of the clinical evaluation. (See 'Testing' above.)

- **Role of supplementation of various vitamins in disease prevention –** There is limited evidence to support vitamin supplementation in the prevention of various conditions.

  - **Folate –** Folic acid supplementation during pregnancy can prevent neural tube defects. (See 'Folic acid' above and "Preconception and prenatal folic acid supplementation", section on 'Folic acid supplementation for preventing NTDs'.)

  - **Vitamin D –** Subclinical vitamin D deficiency may contribute to the development of osteoporosis, falls, and fractures in older adults. Vitamin D supplementation may attenuate bone loss, reduce fracture risk, and reduce falls in deficient persons. (See 'Vitamin D' above and "Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment" and "Calcium and vitamin D supplementation in osteoporosis".)

  - **Antioxidants –** Although diets high in vegetables and fruits that are rich in antioxidants are associated with a reduced risk of cancer and cardiovascular disease (CVD), there is no evidence to support the use of antioxidant supplements to prevent cancer or atherosclerotic CVD. (See "Overview of vitamin A" and "Overview of vitamin E".)

- Vitamin A and the carotenoids – In resource-limited regions, vitamin A supplementation in children ages 6 to 59 months is advised as it is associated with decreased mortality. (See "Overview of vitamin A", section on 'Targeted supplementation for disease'.)

  In some adult populations, supplementation with carotenoids is associated with increased mortality, risk of cancer, risk of osteopenia, and fractures. Vitamin A in high doses (ie, >10,000 international units) taken during the first trimester of pregnancy has been shown to increase the risk of congenital anomalies. (See 'Vitamin A and the carotenoids' above.)

- **Vitamin C –** There is no evidence that vitamin C supplementation reduces cancer, CVD, or mortality risk. Vitamin C supplementation may also increase the risk for oxalate kidney stones. (See 'Vitamin C' above.)

- **Vitamin E –** Evidence does not support a role for vitamin E supplementation in the prevention or treatment of cancers, CVD, dementia, or infection. Further, high-dose vitamin E (≥400 units daily) might be associated with increased all-cause mortality. (See 'Vitamin E' above.)

- **Vitamin B2 (riboflavin) –** There is no evidence of benefits in supplemental vitamin B2 in healthy people eating a balanced diet. B2 supplementation may have a role in management in adults with episodic migraines. (See 'Vitamin B2 (riboflavin)' above.)

- **Vitamin B6 (**pyridoxine**) –** There is no evidence that vitamin B6 supplementation is associated with a decreased risk of cancer or CVD. (See 'Vitamin B6 (pyridoxine)' above.)

- **Vitamin B12 (cobalamin) –** Vitamin B12 deficiency is associated with neuropsychiatric manifestations and megaloblastic anemia. Vitamin B12 supplementation or testing is reasonable for those at increased risk for poor vitamin B12 intake, those who avoid all meat, fish and poultry, people taking metformin, those with alcohol use disorder, and people with little dietary variation or poor-quality diets (such as some older adults and people experiencing poverty) (algorithm 1).

- **Multivitamins –** In healthy people with adequate dietary intake, we suggest not taking multivitamin supplementation for the prevention of chronic disease (**Grade 2B**). However, multivitamin supplementation is appropriate to consider for patients at risk for vitamin deficiency, such as those with alcohol use disorder, a poor-quality diet with low fruit and vegetable intake, malabsorption, a vegan diet, prior bariatric surgery, certain errors of metabolism, as well as those receiving hemodialysis or parenteral nutrition. In addition, we do not struggle to dissuade patients from taking multivitamins if they wish to do so. (See 'Multivitamins' above.)

- **Concerns over toxicity –** Potentially toxic levels of individual vitamins can be achieved easily among people who take very high-potency vitamins. Water-soluble vitamins (folate, vitamin C, B vitamins) are generally tolerated at high doses; fat-soluble vitamins (vitamins A, D, E, K) are generally more toxic than water-soluble vitamins. (See 'Toxicity at high doses' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Robert H Fletcher, MD, MSc, who contributed to earlier versions of this topic review.

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Topic 5368 Version 76.0

GRAPHICS

Vitamin deficiency syndromes and dietary sources of common vitamins[1]

	Function	Deficiency syndrome	Main sources
Water-soluble			
B1 (thiamine)	Thiamine pyrophosphate	Beriberi - dry (peripheral neuropathy) or wet (heart failure), Wernicke encephalopathy (nystagmus, ophthalmoplegia, ataxia)	Wheat germ, whole grains, dried beans, oatmeal, brown rice, pork, liver, lentils, fish, enriched breakfast cereals
B2 (riboflavin)	Flavine adenine dinucleotide	Nonspecific symptoms including edema of mucus membranes, angular stomatitis, glossitis, and seborrheic dermatitis	Milk products, meat, cheese, eggs, liver, ocean fish, oats, kidney beans, whole grains (quinoa), almonds, chicken breast, enriched breakfast cereals
B3 (niacin, nicotinic acid)	Nicotinamide adenine dinucleotide	Pellagra (dermatitis, diarrhea, dementia)	Peanuts, peas, liver, poultry, tuna, salmon, anchovies, lean meat, brown rice, enriched breakfast cereals
B6 (pyridoxine, pyridoxal)	Transaminase cofactor	Anemia, weakness, insomnia, difficulty walking, nasolabial seborrheic dermatitis, cheilosis, stomatitis	Bananas, chick peas, fortified cereals, yeast, potatoes, brown rice, salmon, chicken, tuna, liver, dark leafy greens, papayas, oranges, breakfast cereals fortified with 25% of daily value (DV)
B12 (cobalamin)	One carbon transfer	Megaloblastic anemia (pernicious anemia), neurologic symptoms (subacute combined degeneration)	Clams, tuna, salmon, liver, egg yolk, beef, lentils, fortified cereals with 25% of DV, turkey, cheddar cheese, nutritional yeast

Folate	One carbon transfer	Megaloblastic anemia	Liver, spinach, avocado, lentils, black-eyed peas, asparagus, brussel sprouts, kidney beans, fortified cereals with 25% of DV
Biotin	Pyruvate carboxylase cofactor	Very rare; thinning of hair, other nonspecific symptoms including altered mental status, myalgia, dysesthesias, anorexia, papulosquamous dermatitis	Liver, egg, salmon, pork hamburger, sunflower seeds, sweet potatoes, almonds, tuna, spinach, broccoli, cheddar cheese
Pantothenate	Coenzyme A	Nonspecific symptoms including paresthesias, dysesthesias ("burning feet"), anemia, gastrointestinal symptoms	Breakfast cereals fortified with 100% DV, shiitake mushrooms, white mushrooms, sunflower seeds, eggs, Greek yogurt, chicken, tuna, avocado, potato, peanuts
C (ascorbate)	Antioxidant, collagen synthesis	Scurvy - fatigue, petechiae, ecchymoses, bleeding gums, depression, dry skin, impaired wound healing	Citrus fruits, red and green peppers, papaya, broccoli, brussel sprouts, strawberries, paprika, kohlrabi
Fat-soluble			
A (retinol, retinal, retinoic acid; including some carotenoids)	Vision, epithelial differentiation, antioxidant	Night blindness, xerophthalmia, keratomalacia, Bitot's spot, follicular hyperkeratosis	Cod-liver oil, liver, sweet potatoes, spinach, pumpkin, carrots, herring, milk products, dark leafy green vegetables, butter, egg yolk
D (cholecalciferol, ergocalciferol)	Prohormone for calcium regulation	Rickets, osteomalacia, craniotabes	Cod-liver oil, fatty fish (salmon, trout, tuna), milk, egg yolk, liver, mushrooms, soy, almond and oat milks fortified with vitamin D, fortified cereals

E (tocopherols)	Antioxidant	Sensory and motor neuropathy, ataxia, retinal degeneration, hemolytic anemia	Sunflower seeds, wheat germ oil, almonds, fortified cereals, hazelnuts, peanut butter/peanuts, sunflower oil, safflower oil, spinach, turnip greens, collard
K (phylloquinone, menaquinone, menadione)	Clotting factors, bone proteins	Hemorrhagic disease	Cooked collard greens, spinach, kale, mustard greens, raw spinach, cooked brussel sprouts, pine nuts, green leaf lettuce, kiwi, natto, edamame, soybean oil, olive oil

Reference:

1. *National Institutes of Health. Dietary supplement fact sheets. Available at: https://ods.od.nih.gov/factsheets/list-all/ (Accessed on August 6, 2022).*

Graphic 79983 Version 10.0

Clinical situations in which vitamin deficiency syndromes occur

Mechanism	Examples
Poor intake	Poverty, limited access to food (eg, food deserts, some older adults who have challenges with meal preparation), poor dentition, alcohol use disorder, restrictive diets (eg, vegan)
Malabsorption	Celiac disease, Crohn disease, short bowel, bariatric surgery, chlorhydria, bacterial overgrowth, chronic use of certain medications
Abnormal losses	Hemodialysis, chronic diarrhea
Abnormal metabolism	Genetic polymorphisms, alcohol use disorder (increases folate metabolism), chronic use of certain medications
Inadequate synthesis	Vitamin D (Northern latitude, homebound)

Graphic 81037 Version 5.0

Dietary Reference Intakes (DRIs): Recommended dietary allowances and adequate intakes of several vitamins in children

	Source of goal*	Child 1 to 3	Female 4 to 8	Male 4 to 8	Female 9 to 13	Male 9 to 13	Female 14 to 18	Male 14 to 18
Vitamins								
Vitamin A, mcg RAE	RDA	300	400	400	600	600	700	900
Vitamin E, mg AT	RDA	6	7	7	11	11	15	15
Vitamin D, international units	RDA	600	600	600	600	600	600	600
Vitamin C, mg	RDA	15	25	25	45	45	65	75
Thiamin, mg	RDA	0.5	0.6	0.6	0.9	0.9	1	1.2
Riboflavin, mg	RDA	0.5	0.6	0.6	0.9	0.9	1	1.3
Niacin, mg	RDA	6	8	8	12	12	14	16
Vitamin B6, mg	RDA	0.5	0.6	0.6	1	1	1.2	1.3
Vitamin B12, mcg	RDA	0.9	1.2	1.2	1.8	1.8	2.4	2.4
Choline, mg	AI	200	250	250	375	375	400	550
Vitamin K, mcg	AI	30	55	55	60	60	75	75
Folate, mcg DFE	RDA	150	200	200	300	300	400	400

RAE: retinol activity equivalents; RDA: recommended dietary allowance; AT: alpha-tocopherol; AI: adequate intake; DFE: dietary folate equivalents.

* 14 g fiber per 1000 kcal = basis for AI for fiber.

References:

1. *Institute of Medicine. Dietary Reference Intakes: The essential guide to nutrient requirements. Washington (DC): The National Academies Press, 2006.*
2. *Institute of Medicine. Dietary Reference Intakes for Calcium and Vitamin D. Washington (DC): The National Academies Press, 2010.*

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Graphic 106207 Version 6.0

Dietary reference intakes of trace elements

Life stage group	Zinc (mg/d)		Selenium (mcg/d)		Iodine (mcg/d)		Copper (mcg/d)		Chromium (mcg/d)	
	RDA* AI¶	ULΔ	RDA/AI¶	UL	RDA/AI¶	UL	RDA/AI¶	UL	RDA/AI¶	UL
Infants										
0 to 6 months	**2**¶	4	**15**¶	45	**110**¶	ND	**200**¶	ND	**0.2**¶	ND
7 to 12 months	**3**	5◊	**20**¶	60	**130**¶	ND	**220**¶	ND	**5.5**¶	ND
Children										
1 to 3 years	**3**	7◊	**20**	90	**90**	200	**340**	1000	**11**¶	ND
4 to 8 years	**5**	12◊	**30**	150	**90**	300	**440**	3000	**15**¶	ND
Males										
9 to 13 years	**8**	23◊	**40**	280	**120**	600	**700**	5000	**25**¶	ND
14 to 18 years	**11**	34◊	**55**	400	**150**	900	**890**	8000	**35**¶	ND
19 to 30 years	**11**	40◊	**55**	400	**150**	1100	**900**	10,000	**35**¶	ND
31 to 50 years	**11**	40◊	**55**	400	**150**	1100	**900**	10,000	**35**¶	ND
51 to 70 years	**11**	40◊	**55**	400	**150**	1100	**900**	10,000	**30**¶	ND
>70 years	**11**	40	**55**	400	**150**	1100	**900**	10,000	**30**¶	ND
Females										
9 to 13 years	**8**	23◊	**40**	280	**120**	600	**700**	5000	**21**¶	ND

14 to 18 years	**9**	34◇	**55**	400	**150**	900	**890**	8000	**24**¶	ND
19 to 30 years	**8**	40	**55**	400	**150**	1100	**900**	10,000	**25**¶	ND
31 to 50 years	**8**	40	**55**	400	**150**	1100	**900**	10,000	**25**¶	ND
51 to 70 years	**8**	40	**55**	400	**150**	1100	**900**	10,000	**20**¶	ND
>70 years	**8**	40	**55**	400	**150**	1100	**900**	10,000	**20**¶	ND
Pregnancy										
14 to 18 years	**12**	34	**60**	400	**220**	900	**1000**	8000	**29**¶	ND
19 to 30 years	**11**	40	**60**	400	**220**	1100	**1000**	10,000	**30**¶	ND
31 to 50 years	**11**	40	**60**	400	**220**	1100	**1000**	10,000	**30**¶	ND
Lactation										
14 to 18 years	**13**	34	**70**	400	**290**	900	**1300**	8000	**44**¶	ND
19 to 30 years	**12**	40	**70**	400	**290**	1100	**1300**	10,000	**45**¶	ND
31 to 50 years	**12**	40	**70**	400	**290**	1100	**1300**	10,000	**45**¶	ND

RDA: recommended dietary allowance; AI: adequate intake; UL: upper tolerable level; ND: not determined; WHO: World Health Organization.

* Values in this column represent the RDA, unless otherwise indicated. The RDA is the level of dietary intake that is sufficient to meet the daily nutrient requirements of 97% of the individuals in a specific life stage group.

¶ These values represent the AI. The AI is an approximation of the average nutrient intake that sustains a defined nutritional state, based on observed or experimentally determined values in a defined population.

Δ The UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the specified life stage or gender group.

◇ The ULs for zinc in children set by the WHO are considerably higher than those in this table[1]. The WHO based its UL on estimates of the threshold at which zinc intake alters laboratory measures of copper sufficiency.

References:

1. *Gibson RS, King JC, Lowe N. A Review of Dietary Zinc Recommendations. Food Nutr Bull 2016; 37:443.*

Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Otten JJ, Hellwig JP, Meyers LD (Eds), The National Academies Press, Washington, DC 2006. pp.530-541. Reprinted with permission from the National Academies Press, Copyright © 2006, National Academy of Sciences.

Sources: Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Panthothenic acid, Biotin, and Choline (1998); Dietary reference intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000). These reports may be accessed via www.nap.edu.

Graphic 51953 Version 19.0

Dietary reference intakes for fat-soluble vitamins

Nutrient	Age group	RDA*/AI¶	ULΔ	Adverse effects of excess
Vitamin A				
1 mcg retinol activity equivalent = 3.3 unit vitamin A		**Micrograms daily**	**Micrograms daily**	Ataxia, alopecia, hyperlipidemia, hepatotoxicity, bone and muscle pain; teratogenic
	Infants			
	0 to 6 months	400¶	600	
	7 to 12 months	500¶	600	
	Children			
	1 to 3 years	300	600	
	4 to 8 years	400	900	
	Males			
	9 to 13 years	600	1700	
	14 to 18 years	900	2800	
	≥19 years	900	3000	
	Females			
	9 to 13 years	600	1700	
	14 to 18 years	700	2800	
	≥19 years	700	3000	
	Pregnancy			
	<18 years	750	2800	
	≥19 years	770	3000	
	Lactation			
	<18 years	1200	2800	
	≥19 years	1300	3000	
Vitamin D				
(calciferol) 1 mcg calciferol = 40 int. unit		**Micrograms daily**	**Micrograms daily**	Hypercalcemia, hypercalciuria, polydipsia, polyuria, confusion, anorexia, vomiting
	Infants			
	0 to 12 months	10 (400 int. unit)¶	0 to 6 months: 25 (1000 int. unit)	

			6 to 12 months: 37.5 (1500 int. unit)	bone demineralization
	Children and adolescents			
	1 to 18 years	15 (600 int. unit)	1 to 3 years: 62.5 (2500 int. unit)	
			4 to 8 years: 75 (3000 int. unit)	
			9 to 18 years: 100 (4000 int. unit)	
	Males and females (including pregnancy and lactation)			
	19 to 50 years	15 (600 int. unit)	100 (4000 int. unit)	
	50 to 70 years	15	100	
	>70 years	20 (800 int. unit)	100	
Vitamin E				
(alpha-tocopherol) 1 mg = 1.47 int. unit "natural source" vitamin E or 2.2 int. unit synthetic vitamin E		**Milligrams daily**	**Milligrams daily**	Increased risk of bleeding; possibly increased risk of necrotizing enterocolitis in infants
	Infants			
	0 to 6 months	4[¶]	ND	
	7 to 12 months	5[¶]	ND	
	Children			
	1 to 3 years	6	200	
	4 to 8 years	7	300	
	Males and females (including pregnancy)			
	9 to 13 years	11	600	
	14 to 18 years	15	800	
	>18 years	15	1000	
	Lactation			
	≤18 years	19	800	
	>19 years	19	1000	
Vitamin K				
		Micrograms daily	**Micrograms daily**	No adverse effects associated with vitamin K consumption from food or
	Infants			
	0 to 6 months	2[¶]	ND	
	7 to 12 months	2.5[¶]	ND	

	Children			supplements have been reported; however, data are limited
	1 to 3 years	30¶	ND	
	4 to 8 years	55¶	ND	
	Males			
	9 to 13 years	60¶	ND	
	14 to 18 years	75¶	ND	
	>19 years	120¶	ND	
	Females (including pregnancy and lactation)			
	9 to 13 years	60¶	ND	
	14 to 18 years	75¶	ND	
	>19 years	90¶	ND	

Vitamin A doses given as 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; UL: upper tolerable level; int. unit: international units; ND: not determined; RAE: retinol activity equivalents.

* Values in this column represent the RDA unless otherwise indicated. The RDA is the level of dietary intake that is sufficient to meet the daily nutrient requirements of 97% of the individuals in a specific life stage group.

¶ These values represent an AI. The AI represents an approximation of the average nutrient intake that sustains a defined nutritional state, based on observed or experimentally determined values in a defined population.

Δ The UL is the maximum level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the specified life stage or gender group.

Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Otten JJ, Hellwig JP, Meyers LD (Eds), The National Academies Press, Washington, DC 2006. pp.530-541. Modified with permission from the National Academies Press, Copyright © 2006, National Academy of Sciences.

Sources: Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Panthothenic acid, Biotin, and Choline (1998); Dietary reference intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intake reports of the Food and Nutrition Board, Institute of Medicine (2010). These reports may be accessed via www.nap.edu.

Graphic 81151 Version 27.0

Dietary reference intake (DRI) for water-soluble vitamins

Life stage group	Thiamine (mg/day)		Riboflavin (mg/day)		Niacin (mg/day)*		Pantothenic acid (mg/day)		Vitamin B6 (mg/day)		Bi (mcg
	RDA/AI	UL	RDA/AI	UL	RDA/AI	UL	RDA/AI	UL	RDA/AI	UL	RDA/A
Infants											
0 to 6 months	**0.2**¶	ND	**0.3**¶	ND	**2**¶	ND	**1.7**¶	ND	**0.1**¶	ND	**5**¶
7 to 12 months	**0.3**¶	ND	**0.4**¶	ND	**4**¶	ND	**1.8**¶	ND	**0.3**¶	ND	**6**¶
Children											
1 to 3 years	**0.5**	ND	**0.5**	ND	**6**	10	**2**¶	ND	**0.5**	30	**8**¶
4 to 8 years	**0.6**	ND	**0.6**	ND	**8**	15	**3**¶	ND	**0.6**	40	**12**¶
Males											
9 to 13 years	**0.9**	ND	**0.9**	ND	**12**	20	**4**¶	ND	**1**	60	**20**¶
14 to 18 years	**1.2**	ND	**1.3**	ND	**16**	30	**5**¶	ND	**1.3**	80	**25**¶
19 to 30 years	**1.2**	ND	**1.3**	ND	**16**	35	**5**¶	ND	**1.3**	100	**30**¶
31 to 50 years	**1.2**	ND	**1.3**	ND	**16**	35	**5**¶	ND	**1.3**	100	**30**¶
51 to 70 years	**1.2**	ND	**RDA**	ND	**16**	35	**5**¶	ND	**1.7**	100	**30**¶
>70 years	**1.2**	ND	**1.3**	ND	**16**	35	**5**¶	ND	**1.7**	100	**30**¶
Females											
9 to 13 years	**0.9**	ND	**0.9**	ND	**12**	20	**4**¶	ND	**1**	60	**20**¶

14 to 18 years	**1**	ND	**1**	ND	**14**	30	**5**[¶]	ND	**1.2**	80	**25**[¶]
19 to 30 years	**1.1**	ND	**1.1**	ND	**14**	35	**5**[¶]	ND	**1.3**	100	**30**[¶]
31 to 50 years	**1.1**	ND	**1.1**	ND	**14**	35	**5**[¶]	ND	**1.3**	100	**30**[¶]
51 to 70 years	**1.1**	ND	**1.1**	ND	**14**	35	**5**[¶]	ND	**1.5**	100	**30**[¶]
>70 years	**1.1**	ND	**1.1**	ND	**14**	35	**5**[¶]	ND	**1.5**	100	**30**[¶]
Pregnancy											
14 to 18 years	**1.4**	ND	**1.4**	ND	**18**	30	**6**[¶]	ND	**1.9**	80	**30**[¶]
19 to 30 years	**1.4**	ND	**1.4**	ND	**18**	35	**6**[¶]	ND	**1.9**	100	**30**[¶]
31 to 50 years	**1.4**	ND	**1.4**	ND	**18**	35	**6**[¶]	ND	**1.9**	100	**30**[¶]
Lactation											
14 to 18 years	**1.4**	ND	**1.6**	ND	**17**	30	**7**[¶]	ND	**2**	80	**35**[¶]
19 to 30 years	**1.4**	ND	**1.6**	ND	**17**	35	**7**[¶]	ND	**2**	100	**35**[¶]
31 to 50 years	**1.4**	ND	**1.6**	ND	**17**	35	**7**[¶]	ND	**2**	100	**35**[¶]

Dietary reference intakes (DRIs) include the following measures describing optimal nutrient intake:

- **Recommended dietary allowance (RDA)** – The level of dietary intake that is sufficient to meet the daily nutrient requirements of 97% of the individuals in a specific life stage group.
- **Adequate intake (AI)** – An approximation of the average nutrient intake that sustains a defined nutritional state, based on observed or experimentally determined values in a defined population.

- **Upper tolerable level (UL) –** The maximum level of daily nutrient intake that is likely to pose no risk of adverse health effects in almost all individuals in the specified life stage or gender group.

RDAs and AIs may both be used as goals for individual intake. The AI is used when there are insufficient data to determine the RDA for a given nutrient.

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* Niacin is dosed as niacin equivalents (NE), where 1 mg niacin = 60 mg of tryptophan. Infants 0 to 6 months: only preformed niacin (not NE).

¶ As AI.

Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Otten JJ, Hellwig JP, Meyers LD (Eds), The National Academies Press, Washington, DC 2006. pp.530-541. Reprinted and expanded with permission from the National Academies Press,

Sources: Dietary reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Panthothenic acid, Biotin, and Choline (1998); Dietary reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000). These reports may be accessed via www.nap.edu.

Graphic 69963 Version 22.0

Examples of clinical guidelines for folic acid supplementation

Indication for supplementation	Dose (daily)	Start (minimum)	Initial duration*	Recommended by
High risk				
Open NTD any first degree relative of either parent or a personal history of open NTD in either parent[1,2]	4 mg	3 months PTC	12 weeks	SOGC, ACOG
Moderate risk				
Personal or family history of folate-sensitive congenital anomaly other than NTD[2]	1 mg	3 months PTC	12 weeks	SOGC
Family history of NTD (first- or second-degree relative)[2]	1 mg	3 months PTC	12 weeks	SOGC
Type I or II diabetes[2-4]	1 mg	3 months PTC	12 weeks	SOGC
	0.4 mg	1 month PTC	12 weeks	ADA, ACOG
Maternal gastrointestinal malabsorption[2]	1 mg	3 months PTC	12 weeks	SOGC
Medical conditions associated with risk (advanced liver disease, dialysis, alcohol overuse)[2]	1 mg	3 months PTC	12 weeks	SOGC
Low risk				
Pregnancy or potential for pregnancy[1,5,6]	0.4 mg	At least 1 month PTC	12 weeks	ACOG, CDC
	0.4 to 0.8 mg	1 month PTC	First 2 to 3 months of pregnancy	USPSTF

Clinical guidelines vary regarding the dose of folic acid supplementation in females taking antiseizure medications. Refer to UpToDate content on management of epilepsy during preconception, pregnancy, and the postpartum period.

NTD: neural tube defect; PTC: prior to conception; ACOG: American College of Obstetricians and Gynecologists; SOGC: Society of Obstetricians and Gynaecologists of Canada; ADA: American Diabetes Association; USPSTF: United States Preventive Services Task Force; CDC: Centers for Disease Control and Prevention.

* After 12 weeks, supplementation via a routine prenatal vitamin is recommended through the remainder of pregnancy and lactation to fulfill ongoing maternal and fetoplacental folate requirements.

References:

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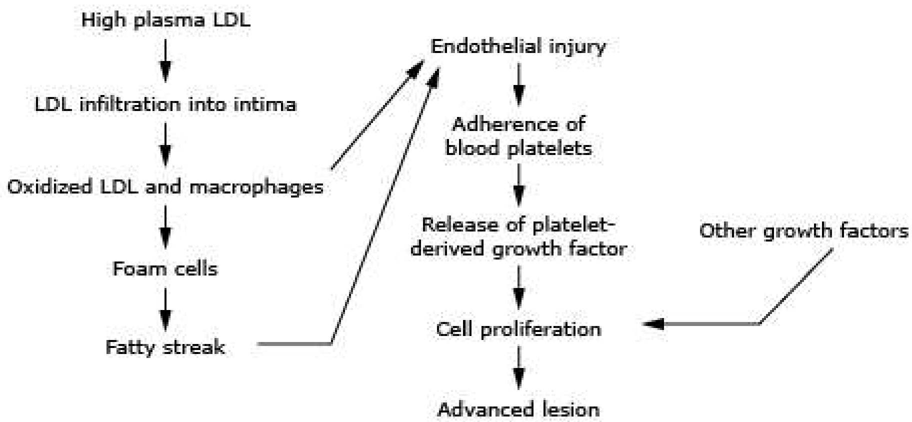
Graphic 111473 Version 9.0

Linkage between lipid infiltration and endothelial injury in atherosclerosis



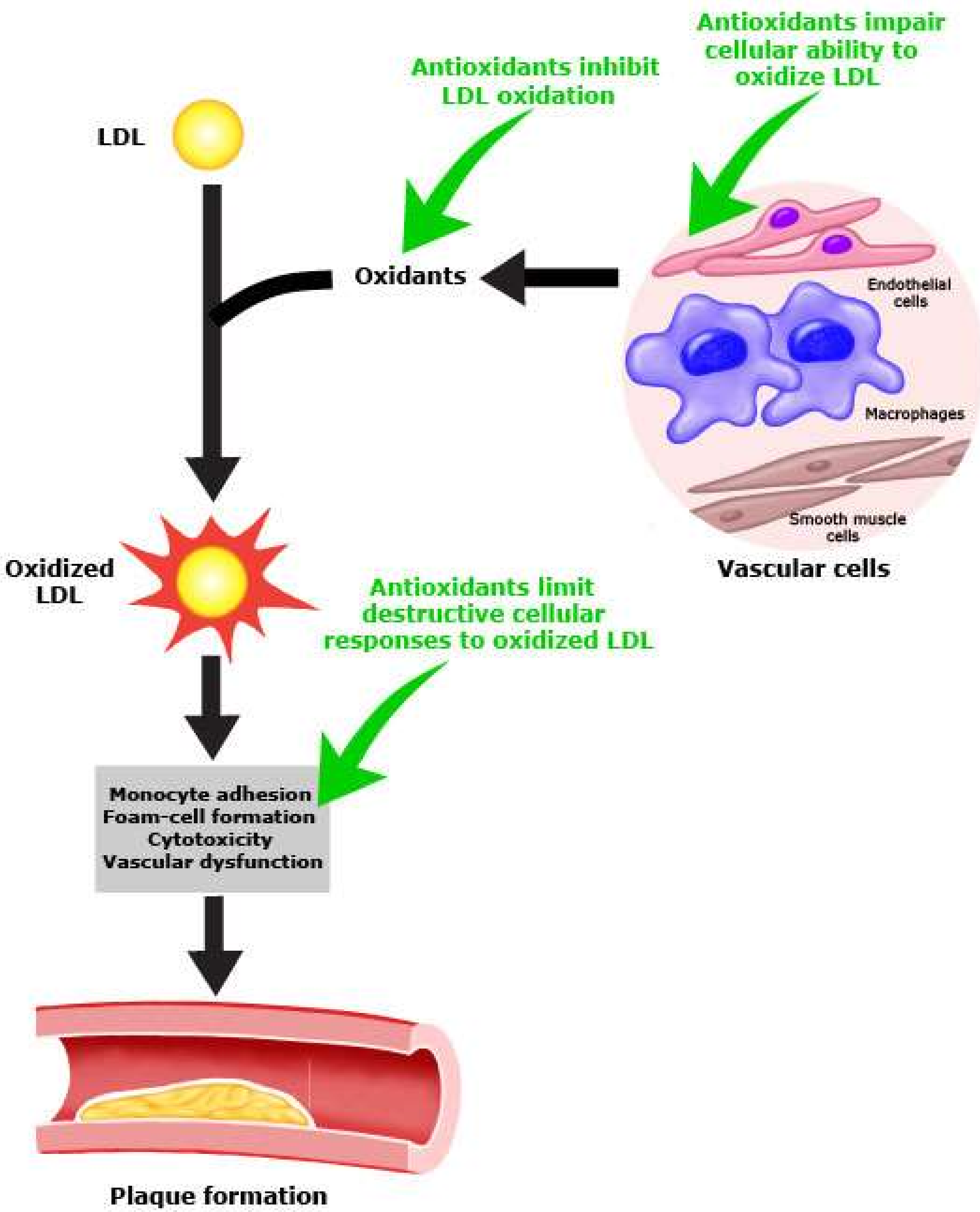
Oxidized LDL in atherosclerosis. Postulated linkage between oxidized LDL and endothelial injury in the pathogenesis of atherosclerosis. Lipid infiltration may be sufficient to account for fatty streaks (left column), while endothelial injury (right column) may account for progression of the fatty streak to more advanced lesions.

LDL: low-density lipoprotein.

Redrawn from Steinberg, D, Parthasarathy, S, Carew, TE, et al, N Engl J Med 1989; 320:915.

Graphic 72955 Version 4.0

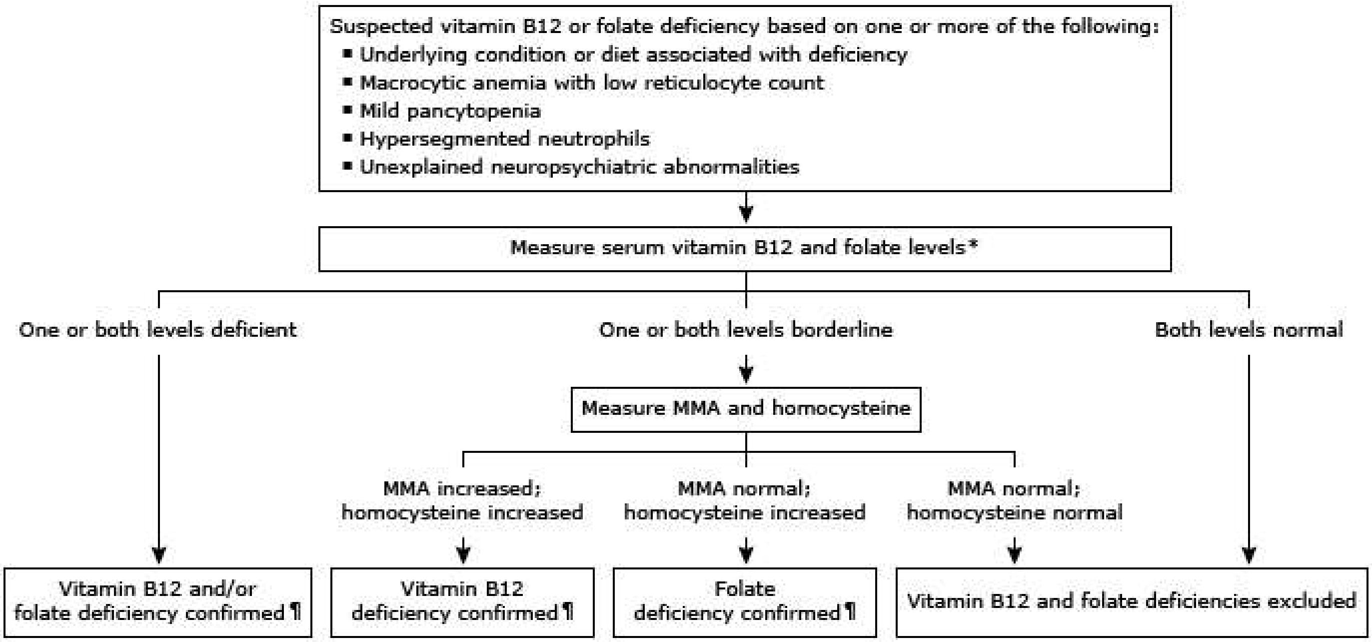
Schematic representation of antioxidant actions



Incorporation of antioxidants into low-density lipoprotein (LDL) protects against oxidation of LDL particles. Additionally, the incorporation of antioxidants into vascular cells may inhibit the vascular response to oxidized LDL.

Graphic 64231 Version 8.0

Diagnostic testing for suspected vitamin B12 or folate deficiency



Some clinicians may choose an alternate testing algorithm depending on patient factors. UpToDate topics on vitamin B12 and folate deficiency discuss the presenting findings, diagnostic approach, differential diagnosis, and treatment in more detail, as well as additional post-diagnostic testing for the underlying causes of these deficiencies. Refer to laboratory-specific lower limits of normal.

- Typical values for vitamin B12 are as follows:
  - Deficient: <200 pg/mL
  - Borderline: 200 to 300 pg/mL
  - Normal: >300 pg/mL
- Typical values for folate are as follows:
  - Deficient: <2 ng/mL
  - Borderline: 2 to 4 ng/mL
  - Normal: >4 ng/mL

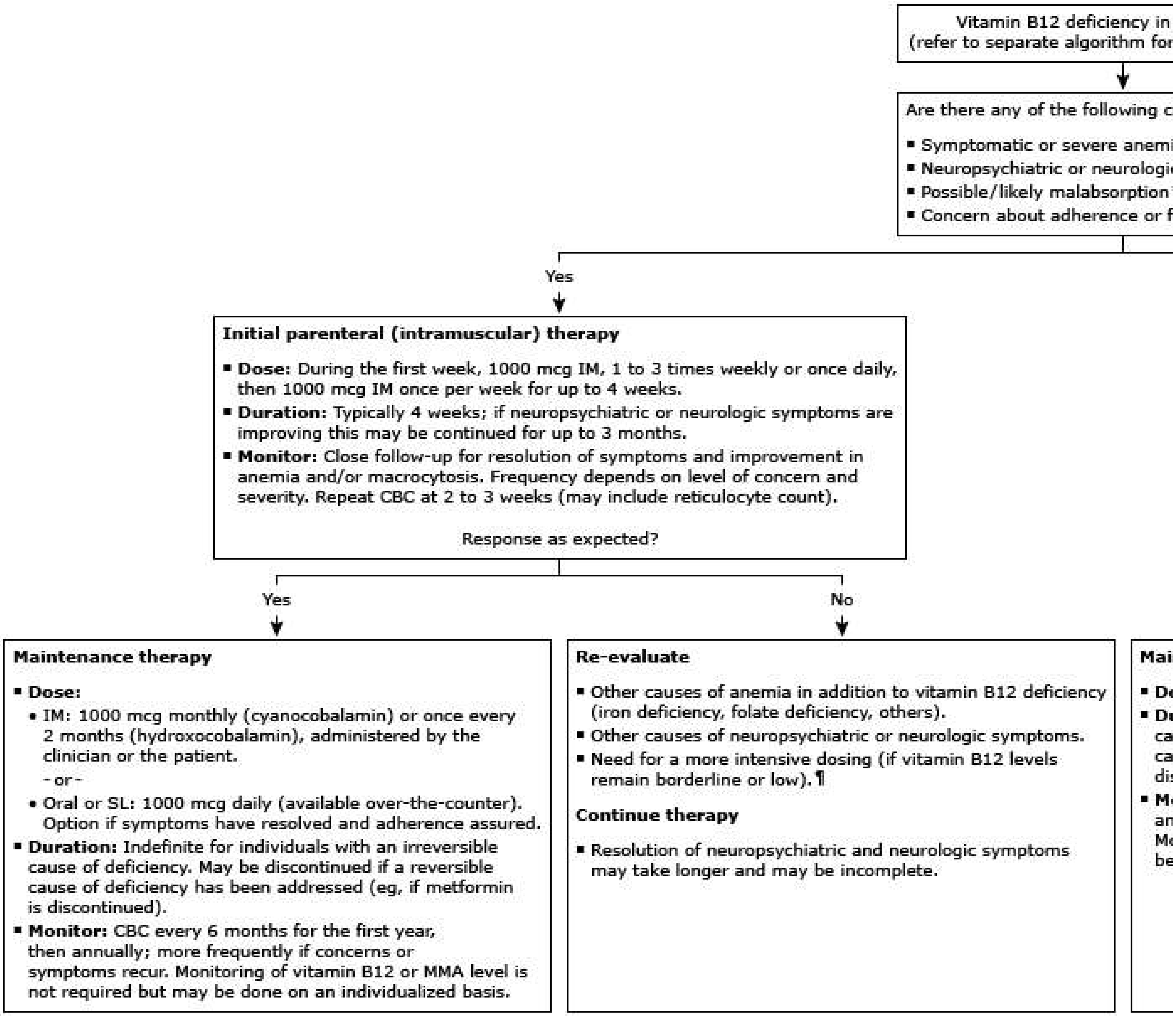
MMA: methylmalonic acid; RBC: red blood cell.

* Folate testing may be omitted if diet and gastrointestinal anatomy and function are normal. If dietary folate deficiency is suspected in a patient who has recently received a normal meal, RBC folate should be measured instead of serum folate. If one level is deficient and the other is borderline, then it may be necessary to follow more than one diagnostic path (eg, if folate is deficient and vitamin B12 is borderline, then folate deficiency may be confirmed but MMA and homocysteine testing may be required to determine vitamin B12 status). Another alternative in this setting would be to administer both vitamins.

¶ Additional testing may be appropriate. Examples include testing of MMA and homocysteine levels to further support a diagnosis of vitamin B12 deficiency; testing for autoantibodies to intrinsic factor if there is vitamin B12 deficiency not attributable to a known gastrointestinal condition; or screening endoscopy for malignancy in individuals with newly diagnosed pernicious anemia.

Graphic 113189 Version 3.0

Treatment of vitamin B12 deficiency in adults



Refer to a separate algorithm for diagnosis of vitamin B12 deficiency, including use of the MMA level in people with borderline vitamin B12 levels. If not known, the cause of vitamin B12 deficiency must be determined as it has implications for the route of administration, duration of therapy, and other testing or treatments that may be indicated. Intranasal, transdermal, and oral "timed release" formulations of vitamin B12 are not recommended, and vitamin B12 is not given intravenously.

Refer to UpToDate for pediatric dosing.

Vitamin B12 administration should lead to a reticulocytosis within several days, improvement in the hemoglobin in 1 to 2 weeks, and normalization of the hemoglobin and MCV within 4 to 8 weeks. Neurologic symptoms may resolve or stabilize without complete resolution. Refer to UpToDate for details.

IM: intramuscular; SL: sublingual; CBC: complete blood count; MMA: methylmalonic acid (increased in vitamin B12 deficiency); MCV: mean corpuscular volume.

* Malabsorption is classically due to pernicious anemia (PA; vitamin B12 deficiency caused by autoantibodies to intrinsic factor or gastric parietal cells). Other causes may include bariatric, gastric, or small intestinal surgery. Some experts will use oral vitamin B12 as initial therapy for individuals with malabsorption if they do not have severe anemia or neurologic complications and if adherence was assured. Refer to UpToDate for diagnostic testing for PA and other evaluations.

¶ Dose and frequency depend on the level of concern and the costs and burdens of therapy, with shared decision making. For severe deficiency, daily dosing for the first week can be considered. If a dose increase is needed due to insufficient response, it is reasonable to increase the dosing frequency (eg, 1000 mcg IM every 2 weeks) and/or increase the dose (eg, 2000 mcg orally instead of 1000 mcg). Lower doses are used for children (refer to UpToDate for details).

Graphic 131424 Version 9.0

Contributor Disclosures

Kathleen M Fairfield, MD, DrPH No relevant financial relationship(s) with ineligible companies to disclose. **Christine C Tangney, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Robert S Rosenson, MD** Equity Ownership/Stock Options: MediMergent, LLC [Pharmacy Claims]. Grant/Research/Clinical Trial Support: Amgen [Lipids]; Arrowhead [Lipids]; Eli Lilly [Lipids]; Novartis [Lipids]; Regeneron [Lipids]. Consultant/Advisory Boards: Amgen [Lipids]; Arrowhead [Lipids]; Avilar Therapeutics [Lipids]; CRISPR Therapeutics [Lipids]; Editas [Lipids]; Lilly [Lipids]; Lipigon [Lipids]; Novartis [Lipids]; Precision Biosciences [Lipids]; Regeneron [Lipids]; Verve Therapeutics [Lipids]. Other Financial Interest: Meda Pharmaceuticals [Lipids, non-promotional lecture]. All of the relevant financial relationships listed have been mitigated. **David Seres, MD** Equity Ownership/Stock Options: Biomed Industries, Inc. [Biomedical informatics, drug development (Alzheimer's and obesity)]. Grant/Research/Clinical Trial Support: Nasotrak Medical Pte, Ltd [Feeding tube technology, safety study]. Consultant/Advisory Boards: Community Surgical Supply [Outpatient infusion pharmacy and DME, parenteral nutrition]. All of the relevant financial relationships listed have been mitigated. **Bernard J Gersh, MB, ChB, DPhil, FRCP, MACC** Consultant/Advisory Boards: Baim Institute [CRO for trials involving Edwards percutaneous valve devices]; Cardiovascular Research Foundation [Data safety monitoring board (RELIEVE-HF Trial)]; Caristo Diagnostics Limited [Imaging and inflammation/atherosclerosis]. All of the relevant financial relationships listed have been mitigated. **Sara Swenson, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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