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Vitamin supplementation in healthy patients: What does the evidence support?

This review, with handy tables, summarizes which vitamins offer proven benefits—and which don't.

Since their discovery in the early 1900s as the treatment for life-threatening deficiency syndromes, vitamins have been touted as panaceas for numerous ailments. While observational data have suggested potential correlations between vitamin status and every imaginable disease, randomized controlled trials (RCTs) have generally failed to find benefits from supplementation. Despite this lack of proven efficacy, more than half of older adults reported taking vitamins regularly.[1]

While most clinicians consider vitamins to be, at worst, expensive placebos, the potential for harm and dangerous interactions exists. Unlike pharmaceuticals, vitamins are generally unregulated, and the true content of many dietary supplements is often difficult to elucidate. Understanding the physiologic role, foundational evidence, and specific indications for the various vitamins is key to providing the best recommendations to patients.

Vitamins are essential organic nutrients, required in small quantities for normal metabolism. Since they are not synthesized endogenously, they must be ingested via food intake. In the developed world, vitamin deficiency syndromes are rare, thanks to sufficiently balanced diets and availability of fortified foods. The focus of this article will be on vitamin supplementation in healthy patients with well-balanced diets. **TABLE W1**[2] (available at mdedge.com/familymedicine) lists the 13 recognized vitamins, their recommended dietary allowances, and any known toxicity risks. **TABLE 2**[2] outlines elements of the history to consider when evaluating for deficiency. A summary of the most clinically significant evidence for vitamin supplementation follows; a more comprehensive review can be found in **TABLE 3**.[3-96]

GRADE DEFINITIONS
For an explanation of USPSTF grade definitions, see **www.uspreventiveservicestaskforce.org/uspstf/about-uspstf/methods-and-processes/grade-definitions**

B COMPLEX VITAMINS

Vitamin B1

- **Vitamers:** Thiamine (thiamin)
- **Physiologic role:** Critical in carbohydrate and amino-acid catabolism and energy metabolism
- **Dietary sources:** Whole grains, meat, fish, fortified cereals, and breads

Thiamine serves as an essential cofactor in energy metabolism.[2] Thiamine deficiency is responsible for beriberi syndrome (rare in the developed world) and Wernicke-Korsakoff syndrome, the latter of which is a relatively common complication of chronic alcohol dependence. Although thiamine's administration in these conditions can be curative, evidence is lacking to support its use preventively in patients with alcoholism.[3] Thiamine has additionally been theorized to play a role in cardiac and cognitive function, but RCT data has not shown consistent patient-oriented benefits.[4,5]

THE TAKEAWAY: Given the lack of evidence, supplementation in the general population is not recommended.

Vitamin B2

- **Vitamers:** Riboflavin
- **Physiologic role:** Essential component of cellular function and growth, energy production, and metabolism of fats and drugs
- **Dietary sources:** Eggs, organ meats, lean meats, milk, green vegetables, fortified cereals and grains

Riboflavin is essential to energy production, cellular growth, and metabolism.[2]

THE TAKEAWAY: Its use as migraine prophylaxis has limited data,[97] but there is otherwise no evidence to support health benefits of riboflavin supplementation.

Vitamin B3

- **Vitamers:** Nicotinic acid (niacin); nicotinamide (niacinamide); nicotinamide riboside
- **Physiologic role:** Converted to nicotinamide adenine dinucleotide (NAD), which is widely required in most cellular metabolic redox processes. Crucial to the synthesis and metabolism of carbohydrates, fatty acids, and proteins
- **Dietary sources:** Poultry, beef, fish, nuts, legumes, grains. (Tryptophan can also be converted to NAD.)

Niacin is readily converted to NAD, an essential coenzyme for multiple catalytic processes in the body. While niacin at doses more than 100 times the recommended dietary allowance (RDA; 1-3 g/d) has been extensively studied for its role in dyslipidemias,[2] pharmacologic dosing is beyond the scope of this article.

THE TAKEAWAY: There is no evidence supporting a clinical benefit from niacin supplementation.

Vitamin B5

- **Vitamers:** Pantothenic acid; pantethine
- **Physiologic role:** Required for synthesis of coenzyme A (CoA) and acyl carrier protein, both essential in fatty acid and other anabolic/catabolic processes
- **Dietary sources:** Almost all plant/animal-based foods. Richest sources include beef, chicken, organ meats, whole grains, and some vegetables

Pantothenic acid is essential to multiple metabolic processes and readily available in sufficient amounts in most foods.[2] Although limited RCT data suggest pantethine may improve lipid measures,[12,98,99] pantothenic acid itself does not seem to share this effect.

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TABLE 2[2]

Relevant history in the evaluation of potential vitamin deficiency

Historical element	Applicable vitamin(s)
Screening questions	
Are there any food groups that you avoid in their entirety?	Multiple
How often do you eat animal products such as meat or dairy?	Vitamin B12, riboflavin
Chronic conditions	
Chronic kidney disease	Vitamin D
Conditions causing increased utilization: hemolysis, sickle cell anemia, thalassemia, neurologic disorders, exfoliative dermatitis, transplant, chemotherapy	Multiple
Gastrointestinal/malabsorptive conditions	Multiple
Genetic conditions	Multiple
History of gastric bypass	Multiple
Lactation	Multiple
Mental health conditions that limit diet (eg, anorexia, dementia, autism)	Multiple
Pregnancy	Folate
Osteoporosis	Vitamin D
Medications	
Antibiotics (chronic use)	Vitamin K
Antiepileptics	Vitamin B6, folate
Antiretrovirals	Multiple
H2 receptor antagonists	Vitamin B12
Isoniazid	Vitamin B6
Metformin	Vitamin B12
Methotrexate	Vitamin B6
Phenytoin	Vitamin B6
Proton pump inhibitors	Vitamin B12
Vitamin K antagonists	Vitamin K
Social/diet history	
Chronic alcohol use disorder	Multiple
Extreme northern climate	Vitamin D
Institutionalized/homebound	Multiple
Ketogenic diet	B-vitamins
Large amounts of raw egg whites	Biotin
Poverty/homelessness	Multiple
Vegetarian/vegan diet	Vitamin B12, riboflavin

TABLE 3

Vitamin supplementation: The evidence at a glance

Vitamin	Disease/function	Evidence summary	Quality/type of evidence
B1	Wernicke-Korsakoff syndrome	No well-defined, evidence-based regimen for prevention or treatment in people with alcoholism	Cochrane review of RCTs[3]
	HF	Higher prevalence of deficiency among HF patients. Supplementation may improve left ventricular ejection fraction; no effect on mortality or patient-oriented outcomes	Systematic review of RCTs[4]
	Alzheimer disease/ dementia	Data too limited and low quality to draw conclusions	Cochrane review of RCTs[5]
B2	Migraine	400 mg/d reduced migraine frequency (NNT = 2.3 for 50% headache frequency reduction) in adults	1 small RCT[6]
	Cancer	No consistent effect on cancer rates	Large cohort studies[7-11]
B3	Cancer	No effect on cancer rates	Large cohort study[8]
B5	Cardiovascular disease	Pantethine (a form of vitamin B5) reduced LDL 10%-20%, reduced triglycerides 15%-30%, and increased HDL 6%-8%. No mortality or patient-oriented benefits	Systematic review of RCTs[12]
B6	Stroke	In conjunction with B9/B12, found to reduce stroke risk after 5 years of supplementation (HR = 0.75; 95% CI, 0.59-0.97)	1 large RCT[13]
	Cancer	No consistent effect on cancer rates	Multiple systematic reviews/ meta-analyses[14-16]
	Cognitive function	No effect on cognitive function	2 systematic reviews/meta-analyses[17,18]
	Pregnancy-associated nausea and vomiting	Recommended by the American College of Obstetricians and Gynecologists; inconsistent data of benefit	Meta-analysis/society guideline[19,20]
B7	Hair, nail, and skin health	Potential increased nail thickness. Case reports suggest improved hair/skin health.	Small, disease-oriented RCTs, case reports[2]
B9/B12	Preconception	Folate recommended for women of childbearing age; found to reduce risk of neural tube defects (RR = 0.31; 95% CI, 0.17-0.58). No consistent evidence of effect on other birth defects.	Multiple systematic reviews/ meta-analyses[21-26]
	Cancer	Inconsistent evidence on effects in cancer; some studies have shown increased risk of colon cancer	Multiple systematic reviews/ meta-analyses[27-29,30]
	Cardiovascular disease	No effect on cardiovascular events or mortality	Multiple systematic reviews/ meta-analyses[31,32]
	Cognitive function	No consistent effect on cognitive function	Multiple systematic reviews/ meta-analyses[18,33-35]
	Fractures	No evidence of decreased fracture risk	Large RCTs[29,36]
Antioxidants (A, E, and C)	AMD	Small reduction in risk of advanced AMD when combined with zinc (OR = 0.72; 95% CI, 0.52-0.98)	Large RCT[37]
	Cancer	Observational data suggest slightly decreased colon cancer risk associated with vitamin C and E. RCT data show no effect of supplementation on cancer rates	Large RCT, 2 pooled analyses of cohort studies[38-40]
	Cardiovascular disease	No association with cardiovascular disease	Systematic review[41]
	Cataracts	No effect on age-related cataracts	Cochrane review of RCTs[42]
	Dementia	No effect on risk of Alzheimer disease	2 systematic reviews/meta-analyses[35,43]

THE TAKEAWAY: There is no data that supplementation of any form of vitamin B5 has any patient-oriented clinical benefits.

Vitamin B6

- **Vitamers:** Pyridoxine; pyridoxamine; pyridoxal
- **Physiologic role:** Widely involved coen-

TABLE 3

Vitamin supplementation: The evidence at a glance (*cont'd*)

Vitamin	Disease/function	Evidence summary	Quality/type of evidence
A	Bone density	Retinol supplementation is associated with decreased bone mineral density and in some studies, increased fracture risk	Systematic review[44]
	Cancer	Beta-carotene associated with increased cancer mortality among smokers and asbestos workers. No benefit on cancer rates	Systematic review/meta-analysis[41]
	Childhood mortality	Vitamin A supplementation in children ages 4-60 months reduced mortality 22% (95% CI, 10%-32%) in nations at high risk of vitamin A deficiency	Meta-analysis[45]
E	All-cause mortality	Increased risk of all-cause mortality with supplementation of ≥ 400 IU/d of vitamin E (RR = 1.04; 95% CI 1.01-1.07)	Meta-analysis[46]
	Cancer	No benefit from supplementation on cancer rates. May increase risk of prostate cancer (HR = 1.17; 99% CI, 1.004-1.36)	Systematic review/meta-analysis, RCT[41,47]
C	Common cold	No significant reduction in incidence of cold. May reduce duration by 8% (95% CI, 3%-12%). May decrease incidence in those subjected to brief, intense exercise and/or cold temperatures	Cochrane review of RCTs[48]
D	Fractures/bone density	Vitamin D + calcium supplementation may reduce hip fracture risk in older adults (RR = 0.84; 95% CI, 0.74-0.96). No effect on fracture risk with vitamin D alone	Multiple systematic reviews/ meta-analyses[49-51]
		No significant effect on bone mineral density in healthy children	Multiple systematic reviews/ meta-analyses[52,53]
	Falls	No consistent effect on falls risk in community-dwelling elders. Small reduction in rate of falls among institutionalized elders (RaR, 0.72; 95% CI, 0.55-0.95)	Multiple systematic reviews/ meta-analyses[54-57]
	All-cause mortality	No consistent effect on all-cause mortality	Multiple systematic reviews/ meta-analyses[41,58-62]
	Cancer	No effect on cancer rates	Multiple systematic reviews/ meta-analyses[41,62-66]
	Cardiovascular disease	No effect on cardiovascular disease outcomes	Multiple systematic reviews/ meta-analyses[41,67-69]
		No effect on hypertension	2 systematic reviews/ meta-analyses[70,71]
	Dementia	No effect on cognitive function	2 systematic reviews/meta-analyses[43,72]
	Chronic pain	No effect on chronic pain control or outcomes	Multiple systematic reviews/ meta-analyses[73-75]
	Pregnancy adverse outcomes	Reduction in risk of pre-eclampsia (RR = 0.48; 95% CI, 0.30-0.79). Reduction of risk of low birthweight infants (RR = 0.55; CI, 0.35-0.87). No effect on rates of asthma or allergic disease in infants	Multiple systematic reviews/ meta-analyses[76-82]
	Upper respiratory infections	Reduction in risk of acute respiratory infection (OR = 0.88; 95% CI, 0.81-0.96)	Systematic review/meta-analysis[83]
	Asthma	Reduction in rate of exacerbation requiring corticosteroids (aIRR = 0.74; 95% CI, 0.56-0.97)	Meta-analysis[84]
	Obesity	No effect on BMI	Systematic review/meta-analysis[85]
	Depression	No effect on depression scores or rates	2 systematic reviews/meta-analyses[86,87]
	Diabetes	Low-quality/heterogenous data showing small reduction of A1C in those with type 2 diabetes (–0.32%; 95% CI, –0.53 to –0.10). No effect on rate of progression to diabetes	Systematic review and RCT[88,89]
	Liver disease	No effect on liver-related morbidity or quality of life	Systematic review/meta-analysis[90]

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TABLE 3

Vitamin supplementation: The evidence at a glance (*cont'd)*

Vitamin	Disease/function	Evidence summary	Quality/type of evidence
Vitamin K	Vitamin K deficiency bleeding in newborns	Intramuscular prophylaxis following delivery reduced risk of moderate-to-severe bleeding (RR = 0.19; CI, 0.08 to 0.46; NNT = 74) and reduced risk of bleeding after circumcision (RR = 0.18; CI, 0.08 to 0.42; NNT = 9)	Systematic review of RCTs/ observational studies[91]
	Fractures/bone density	Potential benefit of supplementation on fracture risk (OR = 0.72; 95% CI, 0.55-0.95). Inconsistent data for effect on bone mineral density and vertebral fracture	2 systematic reviews/meta-analyses[92,93]
	Heart disease	Observational data showing potential association between dietary intake and cardiovascular disease risk. No RCT data on supplementation	Systematic review of observational studies[94]
Multivitamins	All-cause mortality	No effect on all-cause mortality	Systematic review of 2 large RCTs[41]
	Cancer	Borderline decrease in cancer rates in men (RR = 0.93; 95% CI, 0.87-0.99). No effect on cancer rates among women or pooled population	Systematic review of 2 large RCTs[41]
	Cognitive function	No effect on cognitive function	Large RCT[95]
	Cataract/AMD	Small reduction in cataract incidence (HR = 0.91; 95% CI, 0.83-0.99). No effect on AMD	Large RCT[96]

aIRR, adjusted incidence rate ratio; AMD, age-related macular degeneration; BMI, body mass index; HDL, high-density lipoprotein; HF, heart failure; HR, hazard ratio; LDL, low-density lipoprotein; NNT, number needed to treat; OR, odds ratio; RaR, rate ratio; RCTs, randomized controlled trials; RR, relative risk.

zyme for cognitive development, neurotransmitter biosynthesis, homocysteine and glucose metabolism, immune function, and hemoglobin formation

Dietary sources: Fish, organ meats, potatoes/starchy vegetables, fruit (other than citrus), and fortified cereals

Pyridoxine is required for numerous enzymatic processes in the body, including biosynthesis of neurotransmitters and homeostasis of the amino acid homocysteine.[2] While overt deficiency is rare, marginal insufficiency may become clinically apparent and has been associated with malabsorption, malignancies, pregnancy, heart disease, alcoholism, and use of drugs such as isoniazid, hydralazine, and levodopa/carbidopa.[2] Vitamin B6 supplementation is known to decrease plasma homocysteine levels, a theorized intermediary for cardiovascular disease; however, studies have failed to consistently demonstrate patient-oriented benefits.[100-102] While observational data has suggested a correlation between vitamin B6 status and cancer risk, RCTs have not supported benefit from supplementation.[14-16] Potential effects of vitamin B6 supplementation on cognitive function have also been studied without observed benefit.[17,18]

THE TAKEAWAY: Vitamin B6 is recommended as a potential treatment option for nausea in pregnancy.[19] Otherwise, vitamin B6 is readily available in food, deficiency is rare, and no patient-oriented evidence supports supplementation in the general population.

Vitamin B7

Vitamers: Biotin

Physiologic role: Cofactor in the metabolism of fatty acids, glucose, and amino acids. Also plays key role in histone modifications, gene regulation, and cell signaling

Dietary sources: Widely available; most prevalent in organ meats, fish, meat, seeds, nuts, and vegetables (eg, sweet potatoes). Whole cooked eggs are a major source, but raw eggs contain avidin, which blocks absorption

Biotin serves a key role in metabolism, gene regulation, and cell signaling.[2] Biotin is known to interfere with laboratory assays—including cardiac enzymes, thyroid studies, and hormone studies—at normal supplementation doses, resulting in both false-positive and false-negative results.[103]

THE TAKEAWAY: No evidence supports the health benefits of biotin supplementation.

Vitamin B9

- **Vitamers:** Folates; folic acid
- **Physiologic role:** Functions as a coenzyme in the synthesis of DNA/RNA and metabolism of amino acids
- **Dietary sources:** Highest content in spinach, liver, asparagus, and brussels sprouts. Generally found in green leafy vegetables, fruits, nuts, beans, peas, seafood, eggs, dairy, meat, poultry, grains, and fortified cereals.

Vitamin B12

- **Vitamers:** Cyanocobalamin; hydroxocobalamin; methylcobalamin; adenosylcobalamin
- **Physiologic role:** Required for red blood cell formation, neurologic function, and DNA synthesis
- **Dietary sources:** Only in animal products: fish, poultry, meat, eggs, and milk/dairy products. Not present in plant foods. Fortified cereals, nutritional yeast are sources for vegans/vegetarians.

Given their linked physiologic roles, vitamins B9 and B12 are frequently studied together. Folate and cobalamins play key roles in nucleic acid synthesis and amino acid metabolism, with their most clinically significant role in hematopoiesis. Vitamin B12 is also essential to normal neurologic function.[2]

The US Preventive Services Task Force (USPSTF) recommends preconceptual folate supplementation of 0.4-0.8 mg/d in women of childbearing age to decrease the risk of fetal neural tube defects (grade **A**).[21] This is supported by high-quality RCT evidence demonstrating a protective effect of daily folate supplementation in preventing neural tube defects.[22] Folate supplementation's effect on other fetal birth defects has been investigated, but no benefit has been demonstrated. While observational studies have suggested an inverse relationship with folate status and fetal autism spectrum disorder,[23-25] the RCT data is mixed.[26]

A potential role for folate in cancer prevention has been extensively investigated. An expert panel of the National Toxicology Program (NTP) concluded that folate supplementation does not reduce cancer risk in people with adequate baseline folate status based on high-quality meta-analysis data.[27,104] Conversely, long-term follow-up from RCTs demonstrated an increased risk of colorectal adenomas and cancers,[28,29] leading the NTP panel to conclude there is sufficient concern for adverse effects of folate on cancer growth to justify further research.[104]

Given folate and vitamin B12's homocysteine-reducing effects, it has been theorized that supplementation may protect from cardiovascular disease. However, despite extensive research, there remains no consistent patient-oriented outcomes data to support such a benefit.[31,32,105]

The evidence is mixed but generally has found no benefit of folate or vitamin B12 supplementation on cognitive function.[18,33-35] Finally, RCT data has failed to demonstrate a reduction in fracture risk with supplementation.[36,106]

THE TAKEAWAY: High-quality RCT evidence demonstrates a protective effect of preconceptual daily folate supplementation in preventing neural tube defects.[22] The USPSTF recommends preconceptual folate supplementation of 0.4-0.8 mg/d in women of childbearing age to decrease the risk of fetal neural tube defects.

ANTIOXIDANTS

In addition to their individual roles, vitamins A, E, and C are antioxidants, functioning to protect cells from oxidative damage by free radical species.[2] Due to this shared role, these vitamins are commonly studied together. Antioxidants are hypothesized to protect from various diseases, including cancer, cardiovascular disease, dementia, autoimmune disorders, depression, cataracts, and age-related vision decline.[2,37,107-112]

Though observational studies have found a correlation of increased risk for disease with lower antioxidant serum levels, RCTs have not demonstrated a reduction in disease risk with supplementation and, in some cases, have found an increased risk of mortality. While several studies have found potential benefit of antioxidant use in reducing colon and breast cancer risk,[38,113-115] vitamins A and E have been associated with increased risk of lung and prostate cancer, respectively.[47,110] Cardiovascular disease and

While observational studies have found a correlation of increased risk for disease with lower antioxidant serum levels, RCTs have not demonstrated a reduction in disease risk with supplementation.

antioxidant vitamin supplementation has similar inconsistent data, ranging from slight benefit to harm.[2,116] After a large Cochrane review in 2012 found a significant increase in all-cause mortality associated with vitamin E and beta-carotene,[117] the USPSTF made a specific recommendation against supplementation of these vitamins for the prevention of cardiovascular disease or cancer (grade **D**).[118] Given its limited risk for harm, vitamin C was excluded from this recommendation.

Vitamin A

- **Vitamers:** Retinol; retinal; retinyl esters; provitamin A carotenoids (beta-carotene, alpha-carotene, beta-cryptoxanthin)
- **Physiologic role:** Essential for vision and corneal development. Also involved in general cell differentiation and immune function
- **Dietary sources:** Liver, fish oil, dairy, and fortified cereals. Provitamin A sources: leafy green vegetables, orange/yellow vegetables, tomato products, fruits, and vegetable oils

Retinoids and their precursors, carotenoids, serve a critical function in vision, as well as regulating cell differentiation and proliferation throughout the body.[2] While evidence suggests mortality benefit of supplementation in populations at risk of deficiency,[45] wide-ranging studies have found either inconsistent benefit or outright harms in the developed world.

THE TAKEAWAY: Given the USPSTF grade "D" recommendation and concern for potential harms, supplementation is not recommended in healthy patients without risk factors for deficiency.[2]

Vitamin E

- **Vitamers:** Tocopherols (alpha-, beta-, gamma-, delta-); tocotrienol (alpha-, beta-, gamma-, delta-)
- **Physiologic role:** Antioxidant; protects polyunsaturated fats from free radical oxidative damage. Involved in immune function, cell signaling, and regulation of gene expression
- **Dietary sources:** Nuts, seeds, vegetable oil, green leafy vegetables, and fortified cereals

Vitamin E is the collective name of 8 compounds; alpha-tocopherol is the physiologically active form. Vitamin E is involved with cell proliferation as well as endothelial and platelet function.[2]

THE TAKEAWAY: Vitamin E supplementation's effects on cancer, cardiovascular disease, ophthalmologic disorders, and cognition have been investigated; data is either lacking to support a benefit or demonstrates harms as outlined above. Given this and the USPSTF grade "D" recommendation, supplementation is not recommended in healthy patients.[2]

Vitamin C

- **Vitamers:** Ascorbic acid
- **Physiologic role:** Required for synthesis of collagen, L-carnitine, and some neurotransmitters. Also involved in protein metabolism
- **Dietary sources:** Primarily in fruits and vegetables: citrus, tomato, potatoes, red/green peppers, kiwi fruit, broccoli, strawberries, brussels sprouts, cantaloupe, and fortified cereals

Ascorbic acid is a required cofactor for biosynthesis of collagen, neurotransmitters, and protein metabolism.[2] In addition to the shared hypothesized benefits of antioxidants, vitamin C supplementation has undergone extensive research into its potential role in augmenting the immune system and preventing the common cold. Systematic reviews have found daily vitamin C supplementation of at least 200 mg did not affect the incidence of the common cold in healthy adults but may shorten duration and could be of benefit in those exposed to extreme physical exercise or cold.[48] Vitamin C supplementation at the onset of illness does not seem to have benefit.[48] Data is insufficient to draw conclusions about a potential effect on pneumonia incidence or severity.[119,120]

THE TAKEAWAY: Overall, data remain inconclusive as to potential benefits of vitamin C supplementation, although risks of potential harms are likely low.

Vitamin D

- **Vitamers:** Cholecalciferol (D3); ergocalciferol (D2)
- **Physiologic role:** Hydroxylation in liver and kidney required to activate. Promotes dietary

Vitamin C supplementation at the onset of illness does not seem to have benefit.

calcium absorption, enables normal bone mineralization. Also involved in modulation of cell growth, and neuromuscular and immune function

Dietary sources: Few natural dietary sources, which include fatty fish, fish liver oils; small amount in beef liver, cheese, egg yolks. Primary sources include fortified milk and endogenous synthesis in skin with UV exposure

Calciferol is a fat-soluble vitamin required for calcium and bone homeostasis. It is not naturally available in many foods but is primarily produced endogenously in the skin with ultraviolet light exposure.[2]

Bone density and fracture risk reduction are the most often cited benefits of vitamin D supplementation, but this has not been demonstrated consistently in RCTs. Multiple systematic reviews showing inconsistent benefit of vitamin D (with or without calcium) on fracture risk led the USPSTF to conclude that there is insufficient evidence (grade **I**) to issue a recommendation on vitamin D and calcium supplementation for primary prevention of fractures in postmenopausal women.[49-51] Despite some initial evidence suggesting a benefit of vitamin D supplementation on falls reduction, 3 recent systematic reviews did not demonstrate this in community-dwelling elders,[54-56] although a separate Cochrane review did suggest a reduction in rate of falls among institutionalized elders.[57]

THE TAKEAWAY: Given these findings, the USPSTF has recommended against (grade **D**) vitamin D supplementation to prevent falls in community-dwelling elders.[55]

Beyond falls. While the vitamin D receptor is expressed throughout the body and observational studies have suggested a correlation between vitamin D status and many outcomes, extensive RCT data has generally failed to demonstrate extraskeletal benefits from supplementation. Meta-analysis data have demonstrated potential reductions in acute respiratory infection rates and asthma exacerbations with vitamin D supplementation. There is also limited evidence suggesting a reduction in preeclampsia and low-birthweight infant risk with vitamin D supplementation in pregnancy. However, several large meta-analyses and systematic reviews have investigated vitamin D supplementation's effect on all-cause mortality and found no consistent data to support an association.[41,58-62]

Multiple systematic reviews have investigated and found high-quality evidence demonstrating no association between vitamin D supplementation and cancer[41,63-66,121] or cardiovascular disease risk.[41,70,71] There is high-quality data showing no benefit of vitamin D supplementation for multiple additional diseases, including diabetes, cognitive decline, depression, pain, obesity, and liver disease.[43,72-75,85-90,122]

THE TAKEAWAY: Due to poor availability in breastmilk, the American Academy of Pediatrics (AAP) recommends supplementing exclusively breastfed infants with 400 IU/d of vitamin D to prevent rickets.[123] RCT data support high-dose supplementation of lactating women (6400 IU/d) as an alternative strategy to supplementation of the infant.[124] The AAP recommends that all nonbreastfeeding infants and older children ingesting < 1000 mL/d of vitamin D–fortified formula or milk should also be supplemented with 400 IU/d of vitamin D.[123] Despite these universal recommendations for supplementation, evidence is mixed on the effect of vitamin D supplementation on bone health in children.[52,53]

Although concerns about vitamin D supplementation and increased risk of urolithiasis and hypercalcemia have been raised,[51,62,121] systematic reviews have not demonstrated significant, clinically relevant risks, even with high-dose supplementation (> 2800 IU/d).[125,126]

The AAP recommends supplementing exclusively breastfed infants with 400 IU/d of vitamin D to prevent rickets.

Vitamin K

Vitamers: Phylloquinone (K1); menaquinones (K2)

Physiologic role: Coenzyme for synthesis of proteins involved in hemostasis and bone metabolism

Dietary sources: Phylloquinone is found in green leafy vegetables, vegetable oils, some fruits, meat, dairy, and eggs. Menaquinone is produced by gut bacteria and present in fermented foods

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Vitamin K includes 2 groups of similar compounds: phylloquinone and menaquinones. Unlike other fat-soluble vitamins, vitamin K is rapidly metabolized and has low tissue storage.[2]

Administration of vitamin K 0.5 to 1 mg intramuscularly (IM) to newborns is standard of care for the prevention of vitamin K deficiency bleeding (VKDB). This is supported by RCT data demonstrating a reduction in classic VKDB (occurring within 7 days)[91] and epidemiologic data from various countries showing a reduction in late-onset VKDB with vitamin K prophylaxis programs.[127] Oral dosing appears to reduce the risk of VKDB in the setting of parental refusal but is less effective than IM dosing.[128,129]

Vitamin K's effects on bone density and fracture risk have also been investigated. Systematic reviews have demonstrated a reduction in fracture risk with vitamin K supplementation,[92,93] and European and Asian regulatory bodies have recognized a potential benefit on bone health.[2] The FDA considers the evidence insufficient at this time to support such a claim.[2] Higher dietary vitamin K consumption has been associated with lower risk of cardiovascular disease in observational studies[94] and supplementation was associated with improved disease measures,[130] but no patient-oriented outcomes have been demonstrated.[131]

THE TAKEAWAY: The administration of vitamin K 0.5 to 1 mg intramuscularly (IM) to newborns is standard of care for the prevention of VKDB. Vitamin K may lead to a reduction in fracture risk, but the FDA considers the evidence insufficient. Vitamin K's potential link to a lowered risk of cardiovascular disease has not been demonstrated with patient-oriented outcomes. Vitamin K has low potential for toxicity, although its interaction with vitamin K antagonists (ie, warfarin) is clinically relevant.

MULTIVITAMINS

Multivitamins are often defined as a supplement containing 3 or more vitamins and minerals but without herbs, hormones, or drugs.[132] Many multivitamins do contain additional substances, and some include levels of vitamins that exceed the RDA or even the established tolerable upper intake level.[133]

A 2013 systematic review found limited evidence to support any benefit from multivitamin supplementation.[41] Two included RCTs demonstrated a narrowly significant decrease in cancer rates among men, but saw no effect in women or the combined population.[134,135] This benefit appears to disappear at 5 years of follow-up.[136] RCT data have shown no benefit of multivitamin use on cognitive function,[95] and high-quality data suggest there is no effect on all-cause mortality.[137] Given this lack of supporting evidence, the USPSTF has concluded that there is insufficient evidence (grade **I**) to recommend vitamin supplementation in general to prevent cardiovascular disease or cancer.[41]

The use of prenatal multivitamins is generally recommended in the pregnancy and preconception period and has been associated with reduced risk of autism spectrum disorders, pediatric cancer rates, small-for-gestational-age infants, and multiple birth defects in offspring; however, studies have not examined if this benefit exceeds that of folate supplementation alone.[138-140] AAP does not recommend multivitamins for children with a well-balanced diet.[141] Of concern, children taking multivitamins were often found to have excess levels of potentially harmful nutrients such as retinol, zinc, and folic acid.[142]

Children taking multivitamins were often found to have excess levels of potentially harmful nutrients, such as retinol, zinc, and folic acid.

THE TAKEAWAY: There is limited evidence to support any benefit from multivitamin supplementation. Prenatal multivitamins are generally recommended in the pregnancy and preconception period. Overall, the risks of multivitamins are minimal, although that risk is dependent on the multivitamin's constituent components.[143] Components such as vitamin K may interact with a patient's medications, and multivitamins have been shown to reduce the circulating levels of antiretrovirals.[144] Specifically, multivitamins with iron should be avoided in men and postmenopausal women, and safe medication storage should be practiced as multivitamins with iron are a leading cause of poisoning in children.[2]

SUMMARY

Vitamin supplementation in the developed world remains common despite a paucity of RCT data supporting it. Supplementation of folate in women planning to conceive, vitamin D in breastfeeding infants, and vitamin K in newborns are well supported by clinical evidence. Otherwise, there is limited evidence supporting clinically significant benefit from supplementation in healthy patients with well-balanced diets—and in the case of vitamins A and E, there may be outright harms. JFP

CORRESPONDENCE

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TABLE W1

Vitamin overview: RDA and toxicity risk[2]

Fat-soluble vitamins

Vitamin	RDA				
	Infants	*Pediatrics*	*Adults*	*Pregnancy*	*Breastfeeding*
A	400-500 mcg RAE[a,b] (breastmilk) UL = 0.6 mg RAE[b]	300-600 mcg RAE[b] (slice pumpkin pie; 1/2 cup spinach) UL = 0.9 mg RAE[b]	700-900 mcg RAE[b] (1/2 sweet potato; 12 oz herring) UL = 3 mg RAE[b]	770 mcg RAE[b] (2.5 cup French vanilla ice cream) UL = 3 mg RAE[b]	1200-1300 mcg RAE[b] (3/4 oz beef liver) UL = 3 mg RAE[b]
D	400 IU[a] (4 servings fortified cereal + 2 eggs) UL = 1000 IU	600 IU (5 cups vitamin D milk) UL = 1500-3000 IU	600-800 IU (3 oz salmon; 1 cup mushrooms) UL = 4000 IU	600 IU (3 oz rainbow trout) UL = 4000 IU	600 IU (1/2 tbsp cod liver oil) UL = 4000 IU
E	4-5 mg[a] (breastmilk; 1.5 cups cooked spinach)	6-15 mg (1 oz almonds; 2 oz sunflower seeds) UL = 200-600 mg	15 mg (4 oz hazelnuts) UL = 1000 mg	15 mg (7 oz peanuts) UL = 1000 mg	19 mg (1 tbsp wheat germ oil) UL = 1000 mg
K	2 mcg[a] (breastmilk; 1.5 oz mozzarella cheese)	30-60 mcg[a] (1 cup carrot juice; 1.5 cups edamame)	90-120 mcg[a] (1/2 cup cooked broccoli; 1 cup raw spinach)	90 mcg[a] (2 tbsp turnip greens)	90 mcg[a] (1.5 tbsp collard greens)

Water-soluble vitamins

Vitamin	RDA				
	Infants	*Pediatrics*	*Adults*	*Pregnancy*	*Breastfeeding*
B1	0.2-0.3 mg[a] (breastmilk; 1/2 cup acorn squash)	0.5-0.9 mg (1 cup egg noodles; 1 cup black beans	1.1-1.2 mg (1 serving fortified cereal)	1.4 mg (1/2 cup white rice)	1.4 mg (12 oz cooked trout)
B2	0.3-0.4 mg[a] (breastmilk; 2 eggs)	0.4-0.6 mg (2 cups quinoa; 6 oz Swiss cheese)	1.1-1.3 mg (1 cup cooked oats; 1 serving cereal)	1.4 mg (5 oz almonds)	1.6 mg (12 oz steak)
B3	2-4 mg[a] (breastmilk; 1 cup brown rice)	6-12 mg (3 oz pork tenderloin; 5 oz cooked salmon) UL = 10-20 mg	14-16 mg (5 oz turkey breast; 3 cups white rice) UL = 35 mg	18 mg (1 cup marinara sauce) UL = 35 mg	17 mg (9 oz ground beef) UL = 35 mg
B5	1.7-1.8 mg[a] (breastmilk; 4 oz chicken breast)	2-4 mg[a] (0.25-0.5 cup sunflower seeds)	5 mg[a] (fortified breakfast cereal)	6 mg[a] (6 cups broccoli)	7 mg[a] (3.5 avocados)
B6	0.1-0.3 mg[a] (breastmilk; 3 oz ground beef)	0.5-1 mg (3 oz chicken breast; 3 oz cooked tuna) UL = 30-40 mg	1.3-1.7 mg (1-1.5 cups chickpeas) UL = 100 mg	1.9 mg (9 oz salmon) UL = 100 mg	2 mg (6 oz beef liver) UL = 100mg
B7	5-6 mcg[a] (breastmilk; 1 cup sweet potato)	8-20 mcg[a] (5 oz salmon; 2 eggs)	30 mcg[a] (5 cups almonds)	30 mcg[a] (3 eggs)	35 mcg[a] (3.4 oz beef liver)
B9	65-80 mcg DFE[a,b] (breastmilk; 3/4 cup avocado)	150-200 mcg DFE[b] (breakfast cereal; 1 cup white rice) UL = 300-400 mcg DFE[b]	400 mcg DFE[b] (2 cups black-eyed peas) UL = 1000 mcg DFE[b]	600 mcg DFE[b] (2.3 cups cooked spinach) UL = 1000 mcg DFE[b]	500 mcg DFE[b] (6 oz beef liver) UL = 1000 mcg DFE[b]

	Toxicity risks	Notes
	Toxicity with preformed vitamin A; no known risks from excess provitamins. Pseudotumor cerebri, skin irritation, arthralgias, hepatic injury, coma, and death. Congenital birth defects with excess vitamin A/retinoids in pregnancy. Increased mortality with chronic supplementation.	Concomitant use of synthetic retinoids can increase risk of hypervitaminosis A.
	Risk only from excess supplements; no risk with excess sun exposure. Hypercalcemia, nephrocalcinosis, nephrolithiasis, bone demineralization, and cardiovascular calcium deposition.	5-30 min of midday sun exposure to face, arms, and legs twice weekly is sufficient to maintain vitamin D levels.
	High-dose supplementation increases hemorrhage risk. Increased mortality with chronic supplementation.	Large doses with concomitant anticoagulants/antiplatelets can increase bleeding risk. Antioxidants should be avoided with chemotherapy.
	No reported risks associated with vitamin K in humans/animals. Vitamin K antagonizes effect of warfarin.	Chronic antibiotic use can lead to deficiency by eliminating vitamin K–producing GI bacteria.

	Toxicity risks	Notes
	No known toxicity or adverse effects.	Reports of deficient levels with furosemide. Fluorouracil use has been linked to cases of beriberi or Wernicke encephalopathy.
	No known toxicity or adverse effects.	Conversion of tryptophan to NAD and B6 to coenzyme pyridoxal 5′-phosphate are dependent on riboflavin.
	No risk from niacin in food. High supplement/pharmacologic intake: flushing, nausea, paresthesias, headache, dizziness, hypotension, fatigue, insulin resistance, macular edema. Chronic high-dose use: hepatotoxicity.	Isoniazid and pyrazinamide are structural analogs of niacin and interrupt production from tryptophan and conversion to NAD. Large doses can raise blood glucose levels.
	No known toxicity or adverse effects.	
	No risk of toxicity from food sources. Chronic high-dose supplementation: severe/progressive sensory neuropathy, ataxia, painful/disfiguring dermatologic lesions, and photosensitivity.	Vitamin B6 supplementation is recommended with isoniazid use to prevent neuropathy.
	No evidence of toxicity at high doses. May interfere with diagnostic testing, specifically thyroid function tests, pro-BNP, troponins, vitamin D.	Anticonvulsants may increase biotin catabolism and reduce serum levels.
	Limited evidence but concern for: accelerated progression of preneoplastic lesions; immune dysfunction; cognitive impairment in older adults; diminished cognitive development of infants.	High intake of folate may precipitate and/or mask the symptoms of B12 deficiency. Methotrexate is a folate antagonist; folate supplements can interfere with effect.

TABLE W1

Vitamin overview: RDA and toxicity risk[2] *(cont'd)*

Water-soluble vitamins

Vitamin	RDA				
	Infants	*Pediatrics*	*Adults*	*Pregnancy*	*Breastfeeding*
B12	0.4 - 0.5 mcg[a] (breastmilk; 5 oz chicken breast)	0.9-1.2 mcg (1 oz Swiss cheese; 6 oz cured ham)	2.4 mcg (3 oz canned tuna)	2.6 mcg (2 oz cooked trout)	2.8 mcg (6 oz top sirloin cooked)
C	40 – 50 mg[a] (breastmilk; 1 cup raw cauliflower)	15-45 mg (1 raw tomato; 1/2 cup cooked brussels sprouts) UL = 400-650 mg	75-90 mg (1 orange; 1 cup strawberries) UL = 2000 mg	85 mg (1 grapefruit) UL = 2000 mg	120 mg (1 cup raw green peppers) UL = 2000 mg

BNP, B-type natriuretic peptide; DFE, dietary folate equivalents; NAD, nicotinamide adenine dinucleotide; RAE, retinol activity equivalents; RDA, recommended dietary allowance; UL, upper limit.

[a] Adequate intake (AI) – insufficient evidence to establish an RDA.

[b] RDA for vitamin A and folate listed as retinol activity equivalents (RAE) and dietary folate equivalents (DFE) respectively. Vitamers of these vitamins have various levels of activity.

	Toxicity risks	Notes
	No known toxicity or adverse effects.	Deficiency is treated with injectable B12 to avoid potential absorption barriers. High-dose oral treatment may also be effective. Neurologic changes can occur without anemia and be irreversible.
	Low risk of toxicity. Diarrhea, nausea, abdominal cramps. Inconsistent evidence of risk of kidney stones.	Vitamin C content in food is reduced by prolonged storage and cooking. Caution with hemochromatosis; can increase iron absorption. Antioxidants should be avoided with chemotherapy.