

Dietary Supplement Fact Sheet

Vitamin B12

Table of Contents

- Introduction
- Recommended Intakes
- Sources of Vitamin B12
- Vitamin B12 Intakes and Status
- Vitamin B12 Deficiency
- Groups at Risk of Vitamin B12 Deficiency
- Vitamin B12 and Health
- Health Risks from Excessive Vitamin B12
- Interactions with Medications
- Vitamin B12 and Healthful Diets
- References

Introduction

Vitamin B12 is a water-soluble vitamin that is naturally present in some foods, added to others, and available as a dietary supplement and a prescription medication. Vitamin B12 exists in several forms and contains the mineral cobalt [1-4], so compounds with vitamin B12 activity are collectively called "cobalamins". Methylcobalamin and 5-deoxyadenosylcobalamin are the forms of vitamin B12 that are active in human metabolism [5].

Vitamin B12 is required for proper red blood cell formation, neurological function, and DNA synthesis [1-5]. Vitamin B12 functions as a cofactor for methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase catalyzes the conversion of homocysteine to methionine [5,6]. Methionine is required for the formation of S-adenosylmethionine, a universal methyl donor for almost 100 different substrates, including DNA, RNA, hormones, proteins, and lipids. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the degradation of propionate [3,5,6], an essential biochemical reaction in fat and protein metabolism. Succinyl-CoA is also required for hemoglobin synthesis.

Vitamin B12, bound to protein in food, is released by the activity of hydrochloric acid and gastric protease in the stomach [5]. When synthetic vitamin B12 is added to fortified foods and dietary supplements, it is already in free form and, thus, does not require this separation step. Free vitamin B12 then combines with intrinsic factor, a glycoprotein secreted by the stomach's parietal cells, and the resulting complex undergoes absorption within the distal ileum by receptor-mediated endocytosis [5,7]. Approximately 56% of a 1 mcg oral dose of vitamin B12 is absorbed, but absorption decreases drastically when the capacity of intrinsic factor is exceeded (at 1-2 mcg of vitamin B12) [8].

Pernicious anemia is an autoimmune disease that affects the gastric mucosa and results in gastric atrophy. This leads to the destruction of parietal cells, achlorhydria, and failure to produce intrinsic factor, resulting in vitamin B12 malabsorption [3,5,9-11]. If pernicious anemia is left untreated, it causes vitamin B12 deficiency, leading to megaloblastic anemia and neurological disorders, even in the presence of adequate dietary intake of vitamin B12.

Vitamin B12 status is typically assessed via serum or plasma vitamin B12 levels. Values below approximately 170-250 pg/mL (120-180 picomol/L) for adults [5] indicate a vitamin B12 deficiency. However, evidence suggests that serum vitamin B12 concentrations might not accurately reflect intracellular concentrations [6]. An elevated serum homocysteine level (values >13 micromol/L) [12]

might also suggest a vitamin B12 deficiency. However, this indicator has poor specificity because it is influenced by other factors, such as low vitamin B6 or folate levels [5]. Elevated methylmalonic acid levels (values >0.4 micromol/L) might be a more reliable indicator of vitamin B12 status because they indicate a metabolic change that is highly specific to vitamin B12 deficiency [5-7,12].

Recommended Intakes

Intake recommendations for vitamin B12 and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine (IOM) of the National Academies (formerly National Academy of Sciences) [5]. DRI is the general term for a set of reference values used for planning and assessing nutrient intakes of healthy people. These values, which vary by age and gender [5], include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy individuals.
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy.
- Tolerable Upper Intake Level (UL): maximum daily intake unlikely to cause adverse health effects [5].

Table 1 lists the current RDAs for vitamin B12 in micrograms (mcg) [5]. For infants aged 0 to 12 months, the FNB established an AI for vitamin B12 that is equivalent to the mean intake of vitamin B12 in healthy, breastfed infants.

Table 1: Recommended Dietary Allowances (RDAs) for Vitamin B12 [5]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.4 mcg	0.4 mcg		
7-12 months*	0.5 mcg	0.5 mcg		
1-3 years	0.9 mcg	0.9 mcg		
4-8 years	1.2 mcg	1.2 mcg		
9-13 years	1.8 mcg	1.8 mcg		
14+ years	2.4 mcg	2.4 mcg	2.6 mcg	2.8 mcg

* Adequate Intake

Sources of Vitamin B12

Food

Vitamin B12 is naturally found in animal products, including fish, meat, poultry, eggs, milk, and milk products. Vitamin B12 is generally not present in plant foods, but fortified breakfast cereals are a readily available source of vitamin B12 with high bioavailability for vegetarians [5,13-15]. Some nutritional yeast products also contain vitamin B12. Fortified foods vary in formulation, so it is important to read product labels to determine which added nutrients they contain.

Several food sources of vitamin B12 are listed in Table 2.

Table 2: Selected Food Sources of Vitamin B12 [13]

Food	Micrograms (mcg) per serving	Percent DV*

Liver, beef, braised, 1 slice	48.0	800
Clams, cooked, breaded and fried, 3 ounces	34.2	570
Breakfast cereals, fortified with 100% of the DV for vitamin B12, 1 serving	6.0	100
Trout, rainbow, wild, cooked, 3 ounces	5.4	90
Salmon, sockeye, cooked, 3 ounces	4.9	80
Trout, rainbow, farmed, cooked, 3 ounces	4.2	50
Beef, top sirloin, broiled, 3 ounces	2.4	40
Cheeseburger, double patty and bun, 1 sandwich	1.9	30
Breakfast cereals, fortified with 25% of the DV for vitamin B12, 1 serving	1.5	25
Yogurt, plain, 1 cup	1.4	25
Haddock, cooked, 3 ounces	1.2	20
Tuna, white, 3 ounces	1.0	15
Milk, 1 cup	0.9	15
Cheese, Swiss, 1 ounce	0.9	15
Beef taco, 1 taco	0.8	13
Ham, cured, roasted, 3 ounces	0.6	10
Egg, large, 1 whole	0.6	10
Chicken, roasted, ½ breast	0.3	6

*DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration (FDA) to help consumers determine the level of various nutrients in a standard serving of food in relation to their approximate requirement for it. The DV for vitamin B12 is 6.0 mcg. However, the FDA does not require food labels to list vitamin B12 content unless a food has been fortified with this nutrient. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet. The U.S. Department of Agriculture's Nutrient Database Web site (<http://www.nal.usda.gov/fnic/foodcomp/search/> [13]) lists the nutrient content of many foods and provides a comprehensive list of foods containing vitamin B12: <http://www.nal.usda.gov/fnic/foodcomp/Data/SR20/nutrlist/sr20w418.pdf>.

Dietary supplements

In dietary supplements, vitamin B12 is usually present as cyanocobalamin [5], a form that the body readily converts to the active forms methylcobalamin and 5-deoxyadenosylcobalamin. Dietary supplements can also contain methylcobalamin and other forms of vitamin B12.

Existing evidence does not suggest any differences among forms with respect to absorption or bioavailability. However the body's ability to absorb vitamin B12 from dietary supplements is largely limited by the capacity of intrinsic factor. For example, only about 10 mcg of a 500 mcg oral supplement is actually absorbed in healthy people [8].

In addition to oral dietary supplements, vitamin B12 is available in sublingual preparations as tablets or lozenges. These preparations are frequently marketed as having superior bioavailability, although evidence suggests no difference in efficacy between oral and sublingual forms [16,17].

Prescription medications

Vitamin B12, in the form of cyanocobalamin and occasionally hydroxocobalamin, can be administered

parenterally as a prescription medication, usually by intramuscular injection [12]. Parenteral administration is typically used to treat vitamin B12 deficiency caused by pernicious anemia and other conditions that result in vitamin B12 malabsorption and severe vitamin B12 deficiency [12].

Vitamin B12 is also available as a prescription medication in a gel formulation applied intranasally, a product marketed as an alternative to vitamin B12 injections that some patients might prefer [18]. This formulation appears to be effective in raising vitamin B12 blood levels [19], although it has not been thoroughly studied in clinical settings.

Vitamin B12 Intakes and Status

Most children and adults in the United States consume recommended amounts of vitamin B12, according to analyses of data from the 1988-1994 National Health and Nutrition Examination Survey (NHANES III) [5,20] and the 1994-1996 Continuing Survey of Food Intakes by Individuals [5]. Data from the 1999-2000 NHANES indicate that the median daily intake of vitamin B12 for the U.S. population is 3.4 mcg [21].

Some people—particularly older adults, those with pernicious anemia, and those with reduced levels of stomach acidity (achlorhydria) or intestinal disorders—have difficulty absorbing vitamin B12 from food and, in some cases, oral supplements [22,23]. As a result, vitamin B12 deficiency is common, affecting between 1.5% and 15% of the general population [24,25]. In many of these cases, the cause of the vitamin B12 deficiency is unknown [8].

Evidence from the Framingham Offspring Study suggests that the prevalence of vitamin B12 deficiency in young adults might be greater than previously assumed [15]. This study found that the percentage of participants in three age groups (26-49 years, 50-64 years, and 65 years and older) with deficient blood levels of vitamin B12 was similar. The study also found that individuals who took a supplement containing vitamin B12 or consumed fortified cereal more than four times per week were much less likely to have a vitamin B12 deficiency.

Individuals who have trouble absorbing vitamin B12 from foods, as well as vegetarians who consume no animal foods, might benefit from vitamin B12-fortified foods, oral vitamin B12 supplements, or vitamin B12 injections [26].

Vitamin B12 Deficiency

Vitamin B12 deficiency is characterized by megaloblastic anemia, fatigue, weakness, constipation, loss of appetite, and weight loss [1,3,27]. Neurological changes, such as numbness and tingling in the hands and feet, can also occur [5,28]. Additional symptoms of vitamin B12 deficiency include difficulty maintaining balance, depression, confusion, dementia, poor memory, and soreness of the mouth or tongue [29]. The neurological symptoms of vitamin B12 deficiency can occur without anemia, so early diagnosis and intervention is important to avoid irreversible damage [6]. During infancy, signs of a vitamin B12 deficiency include failure to thrive, movement disorders, developmental delays, and megaloblastic anemia [30]. Many of these symptoms are general and can result from a variety of medical conditions other than vitamin B12 deficiency.

Typically, vitamin B12 deficiency is treated with vitamin B12 injections, since this method bypasses potential barriers to absorption. However, high doses of oral vitamin B12 may also be effective. The authors of a review of randomized controlled trials comparing oral with intramuscular vitamin B12 concluded that 2,000 mcg of oral vitamin B12 daily, followed by a decreased daily dose of 1,000 mcg and then 1,000 mcg weekly and finally, monthly might be as effective as intramuscular administration [24,25]. Overall, an individual patient's ability to absorb vitamin B12 is the most important factor in determining whether vitamin B12 should be administered orally or via injection [8]. In most countries, the practice of using intramuscular vitamin B12 to treat vitamin B12 deficiency has remained unchanged [24].

Folic acid and vitamin B12

Large amounts of folic acid can mask the damaging effects of vitamin B12 deficiency by correcting the megaloblastic anemia caused by vitamin B12 deficiency [3,5] without correcting the neurological damage that also occurs [1,31]. Moreover, preliminary evidence suggests that high serum folate levels might not only mask vitamin B12 deficiency, but could also exacerbate the anemia and worsen the cognitive symptoms associated with vitamin B12 deficiency [6,11]. Permanent nerve damage can occur if vitamin B12 deficiency is not treated. For these reasons, folic acid intake from fortified food and supplements should not exceed 1,000 mcg daily in healthy adults [5].

Groups at Risk of Vitamin B12 Deficiency

The main causes of vitamin B12 deficiency include vitamin B12 malabsorption from food, pernicious anemia, postsurgical malabsorption, and dietary deficiency [12]. However, in many cases, the cause of vitamin B12 deficiency is unknown. The following groups are among those most likely to be vitamin B12 deficient.

Older adults

Atrophic gastritis, a condition affecting 10%-30% of older adults, decreases secretion of hydrochloric acid in the stomach, resulting in decreased absorption of vitamin B12 [5,11,32-36]. Decreased hydrochloric acid levels might also increase the growth of normal intestinal bacteria that use vitamin B12, further reducing the amount of vitamin B12 available to the body [37].

Individuals with atrophic gastritis are unable to absorb the vitamin B12 that is naturally present in food. Most, however, can absorb the synthetic vitamin B12 added to fortified foods and dietary supplements. As a result, the IOM recommends that adults older than 50 years obtain most of their vitamin B12 from vitamin supplements or fortified foods [5]. However, some elderly patients with atrophic gastritis require doses much higher than the RDA to avoid subclinical deficiency [38].

Individuals with pernicious anemia

Pernicious anemia, a condition that affects 1%-2% of older adults [11], is characterized by a lack of intrinsic factor. Individuals with pernicious anemia cannot properly absorb vitamin B12 in the gastrointestinal tract [3,5,9,10]. Pernicious anemia is usually treated with intramuscular vitamin B12. However, approximately 1% of oral vitamin B12 can be absorbed passively in the absence of intrinsic factor [11], suggesting that high oral doses of vitamin B12 might also be an effective treatment.

Individuals with gastrointestinal disorders

Individuals with stomach and small intestine disorders, such as celiac disease and Crohn's disease, may be unable to absorb enough vitamin B12 from food to maintain healthy body stores [12,23]. Subtly reduced cognitive function resulting from early vitamin B12 deficiency might be the only initial symptom of these intestinal disorders, followed by megaloblastic anemia and dementia.

Individuals who have had gastrointestinal surgery

Surgical procedures in the gastrointestinal tract, such as weight loss surgery or surgery to remove all or part of the stomach, often result in a loss of cells that secrete hydrochloric acid and intrinsic factor [5,39,40]. This reduces the amount of vitamin B12, particularly food-bound vitamin B12 [41], that the body releases and absorbs. Surgical removal of the distal ileum also can result in the inability to absorb vitamin B12. Individuals undergoing these surgical procedures should be monitored preoperatively and postoperatively for several nutrient deficiencies, including vitamin B12 deficiency [42].

Vegetarians

Strict vegetarians and vegans are at greater risk than lacto-ovo vegetarians and nonvegetarians of developing vitamin B12 deficiency because natural food sources of vitamin B12 are limited to animal foods [5]. Fortified breakfast cereals are one of the few sources of vitamin B12 from plants and can be used as a dietary source of vitamin B12 for strict vegetarians and vegans.

Pregnant and lactating women who follow strict vegetarian diets and their infants

Vitamin B12 crosses the placenta during pregnancy and is present in breast milk. Exclusively breastfed infants of women who consume no animal products may have very limited reserves of vitamin B12 and can develop vitamin B12 deficiency within months of birth [5,43]. Undetected and untreated vitamin B12 deficiency in infants can result in severe and permanent neurological damage.

The American Dietetic Association recommends supplemental vitamin B12 for vegans and lacto-ovo vegetarians during both pregnancy and lactation to ensure that enough vitamin B12 is transferred to the fetus and infant [44]. Pregnant and lactating women who follow strict vegetarian or vegan diets should consult with a pediatrician regarding vitamin B12 supplements for their infants and children [5].

Vitamin B12 and Health

Cardiovascular disease

Cardiovascular disease is the most common cause of death in industrialized countries, such as the United States, and is on the rise in developing countries. Risk factors for cardiovascular disease include elevated low-density lipoprotein (LDL) levels, high blood pressure, low high-density lipoprotein (HDL) levels, obesity, and diabetes [45].

Elevated homocysteine levels have also been identified as an independent risk factor for cardiovascular disease [46-48]. Homocysteine is a sulfur-containing amino acid derived from methionine that is normally present in blood. Elevated homocysteine levels are thought to promote thrombogenesis, impair endothelial vasomotor function, promote lipid peroxidation, and induce vascular smooth muscle proliferation [46,47,49]. Evidence from retrospective, cross-sectional, and prospective studies links elevated homocysteine levels with coronary heart disease and stroke [46,49-58].

Vitamin B12, folate, and vitamin B6 are involved in homocysteine metabolism. In the presence of insufficient vitamin B12, homocysteine levels can rise due to inadequate function of methionine synthase [6]. Results from several randomized controlled trials indicate that combinations of vitamin B12 and folic acid supplements with or without vitamin B6 decrease homocysteine levels in people with vascular disease or diabetes and in young adult women [59-67]. In another study, older men and women who took a multivitamin/multimineral supplement for 8 weeks experienced a significant decrease in homocysteine levels [68].

Evidence supports a role for folic acid and vitamin B12 supplements in lowering homocysteine levels, but results from several large prospective studies have not shown that these supplements decrease the risk of cardiovascular disease [48,62-67]. In the Women's Antioxidant and Folic Acid Cardiovascular Study, women at high risk of cardiovascular disease who took daily supplements containing 1 mg vitamin B12, 2.5 mg folic acid, and 50 mg vitamin B6 for 7.3 years did not have a reduced risk of major cardiovascular events, despite lowered homocysteine levels [65]. The Heart Outcomes Prevention Evaluation (HOPE) 2 trial, which included 5,522 patients older than 54 years with vascular disease or diabetes, found that daily treatment with 2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12 for an average of 5 years reduced homocysteine levels and the risk of stroke but did not reduce the risk of major cardiovascular events [63]. In the Western Norway B Vitamin Intervention Trial, which included 3,096 patients undergoing coronary angiography, daily supplements of 0.4 mg vitamin B12 and 0.8 mg folic acid with or without 40 mg vitamin B6 for 1 year reduced homocysteine levels by 30% but did not affect total

mortality or the risk of major cardiovascular events during 38 months of follow-up [66]. The Norwegian Vitamin (NORVIT) trial [62] and the Vitamin Intervention for Stroke Prevention trial had similar results [67].

The American Heart Association has concluded that the available evidence is inadequate to support a role for B vitamins in reducing cardiovascular risk [48].

Dementia and cognitive function

Researchers have long been interested in the potential connection between vitamin B12 deficiency and dementia [47,69]. A deficiency in vitamin B12 causes an accumulation of homocysteine in the blood [6] and might decrease levels of substances needed to metabolize neurotransmitters [70]. Observational studies show positive associations between elevated homocysteine levels and the incidence of both Alzheimer's disease and dementia [6,47,71]. Low vitamin B12 status has also been positively associated with cognitive decline [72].

Despite evidence that vitamin B12 lowers homocysteine levels and correlations between low vitamin B12 levels and cognitive decline, research has not shown that vitamin B12 has an independent effect on cognition [73-77]. In one randomized, double-blind, placebo-controlled trial, 195 subjects aged 70 years or older with no or moderate cognitive impairment received 1,000 mcg vitamin B12, 1,000 mcg vitamin B12 plus 400 mcg folic acid, or placebo for 24 weeks [73]. Treatment with vitamin B12 plus folic acid reduced homocysteine concentrations by 36%, but neither vitamin B12 treatment nor vitamin B12 plus folic acid treatment improved cognitive function.

Women at high risk of cardiovascular disease who participated in the Women's Antioxidant and Folic Acid Cardiovascular Study were randomly assigned to receive daily supplements containing 1 mg vitamin B12, 2.5 mg folic acid and 50 mg vitamin B6, or placebo [76]. After a mean of 1.2 years, B-vitamin supplementation did not affect mean cognitive change from baseline compared with placebo. However, in a subset of women with low baseline dietary intake of B vitamins, supplementation significantly slowed the rate of cognitive decline. In a trial conducted by the Alzheimer's Disease Cooperative Study consortium that included individuals with mild-to-moderate Alzheimer's disease, daily supplements of 1 mg vitamin B12, 5 mg folic acid, and 25 mg vitamin B6 for 18 months did not slow cognitive decline compared with placebo [77]. Another study found similar results in 142 individuals at risk of dementia who received supplements of 2 mg folic acid and 1 mg vitamin B12 for 12 weeks [75].

The authors of two Cochrane reviews and a systematic review of randomized trials of the effects of B vitamins on cognitive function concluded that insufficient evidence is available to show whether vitamin B12 alone or in combination with vitamin B6 or folic acid has an effect on cognitive function or dementia [78-80]. Additional large clinical trials of vitamin B12 supplementation are needed to assess whether vitamin B12 has a direct effect on cognitive function and dementia [6].

Energy and endurance

Due to its role in energy metabolism, vitamin B12 is frequently promoted as an energy enhancer and an athletic performance and endurance booster. These claims are based on the fact that correcting the megaloblastic anemia caused by vitamin B12 deficiency should improve the associated symptoms of fatigue and weakness. However, vitamin B12 supplementation appears to have no beneficial effect on performance in the absence of a nutritional deficit [81].

Health Risks from Excessive Vitamin B12

The IOM did not establish a UL for vitamin B12 because of its low potential for toxicity. In *Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline*, the IOM states that "no adverse effects have been associated with excess vitamin B12 intake from food and supplements in healthy individuals" [5].

Findings from intervention trials support these conclusions. In the NORVIT and HOPE 2 trials, vitamin B12 supplementation (in combination with folic acid and vitamin B6) did not cause any serious adverse events when administered at doses of 0.4 mg for 40 months (NORVIT trial) and 1.0 mg for 5 years (HOPE 2 trial) [62,63].

Interactions with Medications

Vitamin B12 has the potential to interact with certain medications. In addition, several types of medications might adversely affect vitamin B12 levels. A few examples are provided below. Individuals taking these and other medications on a regular basis should discuss their vitamin B12 status with their healthcare providers.

Chloramphenicol

Chloramphenicol (*Chloromycetin*®) is a bacteriostatic antibiotic. Limited evidence from case reports indicates that chloramphenicol can interfere with the red blood cell response to supplemental vitamin B12 in some patients [82].

Proton pump inhibitors

Proton pump inhibitors, such as omeprazole (*Prilosec*®) and lansoprazole (*Prevacid*®), are used to treat gastroesophageal reflux disease and peptic ulcer disease. These drugs can interfere with vitamin B12 absorption from food by slowing the release of gastric acid into the stomach [83-85]. However, the evidence is conflicting on whether proton pump inhibitor use affects vitamin B12 status [86-89]. As a precaution, health care providers should monitor vitamin B12 status in patients taking proton pump inhibitors for prolonged periods [82].

H2 receptor antagonists

Histamine H2 receptor antagonists, used to treat peptic ulcer disease, include cimetidine (*Tagamet*®), famotidine (*Pepcid*®), and ranitidine (*Zantac*®). These medications can interfere with the absorption of vitamin B12 from food by slowing the release of hydrochloric acid into the stomach. Although H2 receptor antagonists have the potential to cause vitamin B12 deficiency [90], no evidence indicates that they promote vitamin B12 deficiency, even after long-term use [89]. Clinically significant effects may be more likely in patients with inadequate vitamin B12 stores, especially those using H2 receptor antagonists continuously for more than 2 years [90].

Metformin

Metformin, a hypoglycemic agent used to treat diabetes, might reduce the absorption of vitamin B12 [91-93], possibly through alterations in intestinal mobility, increased bacterial overgrowth, or alterations in the calcium-dependent uptake by ileal cells of the vitamin B12-intrinsic factor complex [92,93]. Small studies and case reports suggest that 10%-30% of patients who take metformin have reduced vitamin B12 absorption [92,93]. In a randomized, placebo controlled trial in patients with type 2 diabetes, metformin treatment for 4.3 years significantly decreased vitamin B12 levels by 19% and raised the risk of vitamin B12 deficiency by 7.2% compared with placebo [94]. Some studies suggest that supplemental calcium might help improve the vitamin B12 malabsorption caused by metformin [92,93], but not all researchers agree [95].

Vitamin B12 and Healthful Diets

According to the 2005 Dietary Guidelines for Americans, "nutrient needs should be met primarily through consuming foods. Foods provide an array of nutrients and other compounds that may have beneficial

effects on health. In certain cases, fortified foods and dietary supplements may be useful sources of one or more nutrients that otherwise might be consumed in less than recommended amounts. However, dietary supplements, while recommended in some cases, cannot replace a healthful diet."

The *Dietary Guidelines for Americans* describe a healthy diet as one that:

- Emphasizes a variety of fruits, vegetables, whole grains, and fat-free or low-fat milk and milk products:

Milk and milk products are good sources of vitamin B12. Many ready-to-eat breakfast cereals are fortified with vitamin B12.

- Includes lean meats, poultry, fish, beans, eggs, and nuts.
- Fish and red meat are excellent sources of vitamin B12. Poultry and eggs also contain vitamin B12.
- Is low in saturated fats, trans fats, cholesterol, salt (sodium), and added sugars.
- Stays within your daily calorie needs.

For more information about building a healthful diet, refer to the *Dietary Guidelines for Americans* (<http://www.healthierus.gov/dietaryguidelines/index.html>) and the U.S. Department of Agriculture's food guidance system, *MyPyramid* (<http://www.mypyramid.gov>).

References

1. Herbert V. Vitamin B12 in Present Knowledge in Nutrition. 17th ed. Washington, DC: International Life Sciences Institute Press, 1996.
2. Herbert V, Das K. Vitamin B12 in Modern Nutrition in Health and Disease. 8th ed. Baltimore, MD: Williams & Wilkins, 1994.
3. Combs G. Vitamin B12 in The Vitamins. New York: Academic Press, Inc., 1992.
4. Zittoun J, Zittoun R. Modern clinical testing strategies in cobalamin and folate deficiency. *Sem Hematol* 1999;36:35-46. [PubMed abstract]
5. Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press, 1998.
6. Clarke R. B-vitamins and prevention of dementia. *Proc Nutr Soc* 2008;67:75-81. [PubMed abstract]
7. Klee GG. Cobalamin and folate evaluation: measurement of methylmalonic acid and homocysteine vs vitamin B(12) and folate. *Clin Chem* 2000;46:1277-83. [PubMed abstract]
8. Carmel R. How I treat cobalamin (vitamin B12) deficiency. *Blood*.2008;112:2214-21. [PubMed abstract]
9. Gueant JL, Safi A, Aimone-Gastin I, Rabesona H, Bronowicki J P, Plenat F, et al. Autoantibodies in pernicious anemia type I patients recognize sequence 251-256 in human intrinsic factor. *Proc Assoc Am Physicians* 1997;109:462-9. [PubMed abstract]
10. Kapadia CR. Vitamin B12 in health and disease: part I—inherited disorders of function, absorption, and transport. *Gastroenterologist* 1995;3:329-44. [PubMed abstract]
11. Johnson MA. If high folic acid aggravates vitamin B12 deficiency what should be done about it? *Nutr Rev* 2007;65:451-8. [PubMed abstract]

12. Andrès E, Federici L, Affenberger S, Vidal-Alaball J, Loukili NH, Zimmer J, et al. B12 deficiency: a look beyond pernicious anemia. *J Fam Pract* 2007;56:537-42. [PubMed abstract]
13. U.S. Department of Agriculture, Agricultural Research Service. 2009. USDA National Nutrient Database for Standard Reference, Release 22. Nutrient Data Laboratory Home Page, <http://www.ars.usda.gov/ba/bhnrc/ndl>
14. Subar AF, Krebs-Smith SM, Cook A, Kahle LL. Dietary sources of nutrients among US adults, 1989 to 1991. *J Am Diet Assoc* 1998;98:537-47. [PubMed abstract]
15. Tucker KL, Rich S, Rosenberg I, Jacques P, Dallal G, Wilson WF, et al. Plasma vitamin B12 concentrations relate to intake source in the Framingham Offspring Study. *Am J Clin Nutr* 2000;71:514-22. [PubMed abstract]
16. Yazaki Y, Chow G, Mattie M. A single-center, double-blinded, randomized controlled study to evaluate the relative efficacy of sublingual and oral vitamin B-complex administration in reducing total serum homocysteine levels. *J Altern Complement Med* 2006;12:881-5. [PubMed abstract]
17. Sharabi A, Cohen E, Sulkes J, Garty M. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. *Br J Clin Pharmacol* 2003;56:635-8. [PubMed abstract]
18. Suzuki DM, Alagiakrishnan K, Masaki KH, Okada A, Carethers M. Patient acceptance of intranasal cobalamin gel for vitamin B12 replacement therapy. *Hawaii Med J* 2006;65:311-4. [PubMed abstract]
19. Slot WB, Merkus FW, Van Deventer SJ, Tytgat GN. Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. *Gastroenterology*.1997;113:430-3. [PubMed abstract]
20. Bialostosky K, Wright JD, Kennedy-Stephenson J, McDowell M, Johnson CL. Dietary intake of macronutrients, micronutrients and other dietary constituents: United States 1988-94. *Vital Health Stat* 11 2002;(245):1-158. [PubMed abstract]
21. Ervin RB, Wright JD, Wang CY, Kennedy-Stephenson J. Dietary intake of selected vitamins for the United States population: 1999-2000. *Advance Data from Vital and Health Statistics*; no 339. Hyattsville, Maryland: National Center for Health Statistics. 2004. [\[http://www.cdc.gov/nchs/data/ad/ad339.pdf\]](http://www.cdc.gov/nchs/data/ad/ad339.pdf)
22. Carmel R. Cobalamin, the stomach, and aging. *Am J Clin Nutr* 1997;66:750-9. [PubMed abstract]
23. Carmel R. Malabsorption of food cobalamin. *Baillieres Clin Haematol* 1995;8:639-55. [PubMed abstract]
24. Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. *Cochrane Database Syst Rev* 2005;(3):CD004655. [PubMed abstract]
25. Butler CC, Vidal-Alaball J, Cannings-John R, McCaddon A, Hood K, Papaioannou A, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. *Fam Pract* 2006;23:279-85. [PubMed abstract]
26. Markle HV. Cobalamin. *Crit Rev Clin Lab Sci* 1996;33:247-356. [PubMed abstract]
27. Bernard MA, Nakonezny PA, Kashner TM. The effect of vitamin B12 deficiency on older veterans and its relationship to health. *J Am Geriatr Soc* 1998;46:1199-206. [PubMed abstract]
28. Heaton EB, Savage DG, Brust JC, Garrett TF, Lindenbaum J. Neurological aspects of cobalamin deficiency. *Medicine* 1991;70:229-44.
29. Bottiglieri T. Folate, vitamin B12, and neuropsychiatric disorders. *Nutr Rev* 1996;54:382-90. [PubMed abstract]
30. Monsen ALB, Ueland PM. Homocysteine and methylmalonic acid in diagnosis and risk assessment from infancy to adolescent. *Am J Clin Nutr* 2003;78:7-21. [PubMed abstract]
31. Chanarin I. Adverse effects of increased dietary folate. Relation to measures to reduce the incidence of neural tube defects. *Clin Invest Med* 1994;17:244-52. [PubMed abstract]
32. Huritz A, Brady DA, Schaal SE, Samloff IM, Dedon J, Ruhl CE. Gastric acidity in older adults. *J Am Med Assoc* 1997;278:659-62. [PubMed abstract]
33. Andrews GR, Haneman B, Arnold BJ, Booth JC, Taylor K. Atrophic gastritis in the aged. *Australas Ann Med* 1967;16:230-5. [PubMed abstract]
34. Johnsen R, Bernersen B, Straume B, Forder OH, Bostad L, Burhol PG. Prevalence of endoscopic

- and histological findings in subjects with and without dyspepsia. *Br Med J* 1991;302:749-52. [PubMed abstract]
35. Krasinski SD, Russell R, Samloff IM, Jacob RA, Dalal GE, McGandy RB, et al. Fundic atrophic gastritis in an elderly population: Effect on hemoglobin and several serum nutritional indicators. *J Am Geriatr Soc* 1986;34:800-6. [PubMed abstract]
 36. Carmel R. Prevalence of undiagnosed pernicious anemia in the elderly. *Arch Intern Med* 1996;156:1097-100. [PubMed abstract]
 37. Suter PM, Golner BB, Goldin BR, Morrow FD, Russel RM. Reversal of protein-bound vitamin B12 malabsorption with antibiotics in atrophic gastritis. *Gastroenterology* 1991;101:1039-45. [PubMed abstract]
 38. Carmel R, Sarrai M. Diagnosis and management of clinical and subclinical cobalamin deficiency: advances and controversies. *Curr Hematol Rep* 2006;5:23-33. [PubMed abstract]
 39. Sumner AE, Chin MM, Abraham JL, Gerry GT, Allen RH, Stabler SP. Elevated methylmalonic acid and total homocysteine levels show high prevalence of vitamin B12 deficiency after gastric surgery. *Ann Intern Med* 1996;124:469-76. [PubMed abstract]
 40. Brolin RE, Gorman JH, Gorman RC, Petschenik A J, Bradley L J, Kenler H A, et al. Are vitamin B12 and folate deficiency clinically important after roux-en-Y gastric bypass? *J Gastrointest Surg* 1998;2:436-42. [PubMed abstract]
 41. Doscherholmen A, Swaim WR. Impaired assimilation of egg Co 57 vitamin B 12 in patients with hypochlorhydria and achlorhydria and after gastric resection. *Gastroenterology* 1973;64:913-9. [PubMed abstract]
 42. Commonwealth of Massachusetts, Betsy Lehman Center for Patient Safety and Medical Error Reduction. Expert Panel on Weight Loss Surgery, Executive Report, 2007. [\[http://www.mass.gov/Eeohhs2/docs/dph/patient_safety/weight_loss_executive_report_dec07.pdf\]](http://www.mass.gov/Eeohhs2/docs/dph/patient_safety/weight_loss_executive_report_dec07.pdf)
 43. von Schenck U, Bender-Gotze C, Koletzko B. Persistence of neurological damage induced by dietary vitamin B12 deficiency in infancy. *Arch Dis Childhood* 1997;77:137-9. [PubMed abstract]
 44. Kaiser L, Allen LH. Position of the American Dietetic Association: nutrition and lifestyle for a healthy pregnancy outcome. *J Am Diet Assoc* 2008;108:553-61. [PubMed abstract]
 45. National Institutes of Health. Third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Bethesda, MD: National Cholesterol Education Program, National Heart, Lung, and Blood Institute, National Institutes of Health, September 2002. NIH Publication No. 02-5215.
 46. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, et al. The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. *J Nutr* 2006;136(6 Suppl):1731S-40S. [PubMed abstract]
 47. Schulz RJ. Homocysteine as a biomarker for cognitive dysfunction in the elderly. *Curr Opin Clin Nutr Metab Care* 2007;10:718-23. [PubMed abstract]
 48. American Heart Association Nutrition Committee, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, et al. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. *Circulation* 2006;114:82-96. [PubMed abstract]
 49. Malinow MR. Plasma homocyst(e)ine and arterial occlusive diseases: a mini-review. *Clin Chem* 1995;41:173-6. [PubMed abstract]
 50. Selhub J, Jacques PF, Bostom AG, D'Agostino RB, Wilson PW, Belanger AJ, et al. Association between plasma homocysteine concentrations and extracranial carotid-artery stenosis. *N Engl J Med* 1995;332:286-91. [PubMed abstract]
 51. Rimm EB, Willett WC, Hu FB, Sampson L, Colditz GA, Manson JE, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *J Am Med Assoc* 1998;279:359-64. [PubMed abstract]
 52. Refsum H, Ueland PM, Nygard O, Vollset SE. Homocysteine and cardiovascular disease. *Annu Rev Med* 1998;49:31-62. [PubMed abstract]
 53. Boers GH. Hyperhomocysteinemia: A newly recognized risk factor for vascular disease. *Neth J Med* 1994;45:34-41.

54. Selhub J, Jacques PF, Wilson PF, Rush D, Rosenberg IH. Vitamin status and intake as primary determinants of homocysteinemia in an elderly population. *J Am Med Assoc* 1993;270:2693-8. [PubMed abstract]
55. Flynn MA, Herbert V, Nolph GB, Krause G. Atherogenesis and the homocysteine-folate-cobalamin triad: do we need standardized analyses? *J Am Coll Nutr* 1997;16:258-67. [PubMed abstract]
56. Fortin LJ, Genest J Jr. Measurement of homocyst(e)ine in the prediction of arteriosclerosis. *Clin Biochem* 1995;28:155-62. [PubMed abstract]
57. Siri PW, Verhoef P, Kok FJ. Vitamins B6, B12, and folate: association with plasma total homocysteine and risk of coronary atherosclerosis. *J Am Coll Nutr* 1998;17:435-41. [PubMed abstract]
58. Ubbink JB, van der Merwe A, Delport R, Allen R H, Stabler S P, Riezler R, et al. The effect of a subnormal vitamin B6 status on homocysteine metabolism. *J Clin Invest* 1996;98:177-84. [PubMed abstract]
59. Bronstrup A, Hages M, Prinz-Langenohl R, Pietrzik K. Effects of folic acid and combinations of folic acid and vitamin B12 on plasma homocysteine concentrations in healthy, young women. *Am J Clin Nutr* 1998;68:1104-10. [PubMed abstract]
60. Clarke R. Lowering blood homocysteine with folic acid based supplements. *Br Med J* 1998;316:894-8. [PubMed abstract]
61. Lee BJ, Huang MC, Chung LJ, Cheng CH, Lin KL, Su KH, et al. Folic acid and vitamin B12 are more effective than vitamin B6 in lowering fasting plasma homocysteine concentration in patients with coronary artery disease. *Eur J Clin Nutr* 2004;58:481-7. [PubMed abstract]
62. Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N Engl J Med* 2006;354:1578-88. [PubMed abstract]
63. Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. *N Engl J Med*. 2006;354:1567-77. [PubMed abstract]
64. Clarke R, Lewington S, Sherliker P, Armitage J. Effects of B-vitamins on plasma homocysteine concentrations and on risk of cardiovascular disease and dementia. *Curr Opin Clin Nutr Metab Care* 2007;10:32-9. [PubMed abstract]
65. Albert CM, Cook NR, Gaziano JM, Zaharris E, MacFadyen J, Danielson E, et al. Effect of folic acid and B vitamins on risk of cardiovascular events and total mortality among women at high risk for cardiovascular disease: a randomized trial. *JAMA*.2008;299:2027-36. [PubMed abstract]
66. Ebbing M, Bleie Ø, Ueland PM, Nordrehaug JE, Nilsen DW, Vollset SE, et al. Mortality and cardiovascular events in patients treated with homocysteine-lowering B vitamins after coronary angiography: a randomized controlled trial. *JAMA* 2008;300:795-804. [PubMed abstract]
67. Toole JF, Malinow MR, Chambless LE, Spence JD, Pettigrew LC, Howard VJ, et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomized controlled trial. *JAMA* 2004;291:565-75. [PubMed abstract]
68. McKay DL, Perrone G, Rasmussen H, Dallal G, Blumberg JB. Multivitamin/mineral supplementation improves plasma B-vitamin status and homocysteine concentration in healthy older adults consuming a folate-fortified diet. *J Nutr* 2000;130:3090-6. [PubMed abstract]
69. Carmel R. Megaloblastic anemias. *Curr Opin Hematol* 1994;1:107-12. [PubMed abstract]
70. Hutto BR. Folate and cobalamin in psychiatric illness. *Compr Psychiatry* 1997;38:305-14. [PubMed abstract]
71. Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. *N Engl J Med* 2002;346:476-83. [PubMed abstract]
72. Clarke R, Birks J, Nexø E, Ueland PM, Schneede J, Scott J, et al. Low vitamin B-12 status and risk of cognitive decline in older adults. *Am J Clin Nutr* 2007;86:1384-91. [PubMed abstract]
73. Eussen SJ, de Groot LC, Joosten LW, Bloo RJ, Clarke R, Ueland PM, et al. Effect of oral vitamin B-12 with or without folic acid on cognitive function in older people with mild vitamin B-12 deficiency: a randomized, placebo-controlled trial. *Am J Clin Nutr* 2006;84:361-70. [PubMed abstract]
74. Hvas AM, Juul S, Lauritzen L, Nexø E, Ellegaard J. No effect of vitamin B-12 treatment on

- cognitive function and depression: a randomized placebo controlled study. *J Affect Disord* 2004;81:269-73. [PubMed abstract]
75. Vital Trial Collaborative Group. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *J Intern Med* 2003; 254:67-75. [PubMed abstract]
 76. Kang JH, Cook N, Manson J, Buring JE, Albert CM, Grodstein F. A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease. *Am J Clin Nutr* 2008;88:1602-10. [PubMed abstract]
 77. Aisen PS, Schneider LS, Sano M, Diaz-Arrastia R, van Dyck CH, Weiner MF, et al.; Alzheimer Disease Cooperative Study. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. *JAMA* 2008 ;300:1774-83. [PubMed abstract]
 78. Balk EM, Raman G, Tatsioni A, Chung M, Lau J, Rosenberg IH. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. *Arch Intern Med* 2007 Jan ;167:21-30. [PubMed abstract]
 79. Malouf R, Areosa Sastre A. Vitamin B12 for cognition. *Cochrane Database Syst Rev* 2003;(3):CD004326. [PubMed abstract]
 80. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of health elderly and demented people. *Cochrane Database Syst Rev*. 2008 Oct 8;(4):CD004514. [PubMed abstract]
 81. Lukaski HC. Vitamin and mineral status: effects on physical performance. *Nutrition* 2004;20:632-44. [PubMed abstract]
 82. Natural Medicines Comprehensive Database. Vitamin B12. [<http://www.NaturalDatabase.com>]
 83. Bradford GS and Taylor CT. Omeprazole and vitamin B12 deficiency. *Ann Pharmacother* 1999;33:641-3. [PubMed abstract]
 84. Kasper H. Vitamin absorption in the elderly. *Int J Vitam Nutr Res* 1999;69:169-72. [PubMed abstract]
 85. Howden CW. Vitamin B12 levels during prolonged treatment with proton pump inhibitors. *J Clin Gastroenterol* 2000;30:29-33. [PubMed abstract]
 86. Valuck RJ, Ruscin JM. A case-control study on adverse effects: H2 blocker or proton pump inhibitor use and risk of vitamin B12 deficiency in older adults. *J Clin Epidemiol* 2004;57:422-8. [PubMed abstract]
 87. Ruscin JM, Page RL 2nd, Valuck RJ. Vitamin B(12) deficiency associated with histamine(2)-receptor antagonists and a proton-pump inhibitor. *Ann Pharmacother* 2002;36:812-6. [PubMed abstract]
 88. Den Elzen WP, Groeneveld Y, De Ruijter W, Souverijn JH, Le Cessie S, Assendelft WJ, et al. Long-term use of proton pump inhibitors (PPIs) and vitamin B12 status in elderly individuals. *Aliment Pharmacol Ther* 2008;27:491-7. [PubMed abstract]
 89. Termanini B, Gibril F, Sutliff VE, Yu F, Venzon DJ, Jensen RT. Effect of long-term gastric acid suppressive therapy on serum vitamin B12 levels in patients with Zollinger-Ellison syndrome. *Am J Med* 1998;104:422-30. [PubMed abstract]
 90. Force RW, Nahata MC. Effect of histamine H2-receptor antagonists on vitamin B12 absorption. *Ann Pharmacother* 1992;26:1283-6. [PubMed abstract]
 91. Liu KW, Dai LK, Jean W. Metformin-related vitamin B12 deficiency. *Age Ageing* 2006;35:200-1. [PubMed abstract]
 92. Buvat DR. Use of metformin is a cause of vitamin B12 deficiency. *Am Fam Physician* 2004;69:264. [PubMed abstract]
 93. Bauman WA, Shaw S, Jayatilleke K, Spungen AM, Herbert V. Increased intake of calcium reverses the B12 malabsorption induced by metformin. *Diabetes Care* 2000;23:1227-31. [PubMed abstract]
 94. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ*. 2010 May 20;340:c2181. [PubMed abstract]
 95. Oh R, Brown DL. Use of metformin is a cause of vitamin B12 deficiency. *Author Reply Am Fam*

Physician 2004;69:264, 266. [PubMed abstract]

Disclaimer

Reasonable care has been taken in preparing this document and the information provided herein is believed to be accurate. However, this information is not intended to constitute an "authoritative statement" under Food and Drug Administration rules and regulations.

About ODS

The mission of the Office of Dietary Supplements (ODS) is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

General Safety Advisory

Health professionals and consumers need credible information to make thoughtful decisions about eating a healthful diet and using vitamin and mineral supplements. These Fact Sheets provide responsible information about the role of vitamins and minerals in health and disease. Each Fact Sheet in this series received extensive review by recognized experts from the academic and research communities.

The information is not intended to be a substitute for professional medical advice. It is important to seek the advice of a physician about any medical condition or symptom. It is also important to seek the advice of a physician, registered dietitian, pharmacist, or other qualified health professional about the appropriateness of taking dietary supplements and their potential interactions with medications.

Document Last Updated: 5/26/2010

Office of Dietary Supplements
National Institutes of Health
Bethesda, Maryland 20892 USA
Web: <http://ods.od.nih.gov>
E-mail: ods@nih.gov

