National Institutes of Health
Office of Dietary Supplements

Vitamin B12

Fact Sheet for Health Professionals

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. Because vitamin B12 contains the mineral cobalt, compounds with vitamin B12 activity are collectively called “cobalamins” [1]. Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B12. However, two others forms, hydroxycobalamin and cyanocobalamin, become biologically active after they are converted to methylcobalamin or 5-deoxyadenosylcobalamin [1-3].

Vitamin B12 is required for the development, myelination, and function of the central nervous system; healthy red blood cell formation; and DNA synthesis [1,4,5]. Vitamin B12 functions as a cofactor for two enzymes, methionine synthase and L-methylmalonyl-CoA mutase [1-3,5]. Methionine synthase catalyzes the conversion of homocysteine to the essential amino acid methionine [1,2]. Methionine is required for the formation of S-adenosylmethionine, a universal methyl donor for almost 100 different substrates, including DNA, RNA, proteins, and lipids [3,5]. L-methylmalonyl-CoA mutase converts L-methylmalonyl-CoA to succinyl-CoA in the metabolism of propionate, a short-chain fatty acid [2].

Vitamin B12 is bound to protein in food and must be released before it is absorbed [5]. The process starts in the mouth when food is mixed with saliva. The freed vitamin B12 then binds with haptocorrin, a cobalamin-binding protein in the saliva. More vitamin B12 is released from its food matrix by the activity of hydrochloric acid and gastric protease in the stomach, where it then binds to haptocorrin [1]. In the duodenum, digestive enzymes free the vitamin B12 from haptocorrin, and this freed vitamin B12 combines with intrinsic factor, a transport and delivery binding protein secreted by the stomach’s parietal cells. The resulting complex is absorbed in the distal ileum by receptor-mediated endocytosis [1,5]. If vitamin B12 is added to fortified foods and dietary supplements, it is already in free form and therefore does not require the separation step.

Vitamin B12 status is typically assessed by measurements of serum or plasma vitamin B12 levels. The cutoff between normal vitamin B12 levels and deficiency varies by method and laboratory, but most laboratories define subnormal serum or plasma values as those lower than 200 or 250 pg/mL (148 or 185 pmol/L) [2]. Levels of serum methylmalonic acid (MMA), a vitamin B12-associated metabolite, are the most sensitive markers of vitamin B12 status, and an MMA level greater than 0.271 micromol/L suggests vitamin B12 deficiency [6-8]. However, MMA levels also rise with renal insufficiency and tend to be higher in older adults [6,9,10]. Another marker is total plasma homocysteine levels, which rise quickly as vitamin B12 status declines; a serum homocysteine level higher than 15 micromol/L, for example, suggests vitamin B12 deficiency [11]. However, this indicator has poor specificity because it is influenced by other factors, such as low folate levels and, especially, by declines in kidney function

[6]. Experts suggest that if a patient's serum vitamin B12 level is less than 150 pg/ml (111 pmol/L), the patient's serum MMA levels should be checked to confirm a diagnosis of vitamin B12 deficiency [7,9].

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 National Academies of Sciences, Engineering, and Medicine [1]. 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 sex, include:

- Recommended Dietary Allowance (RDA): Average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%–98%) healthy individuals; often used to plan nutritionally adequate diets for individuals.
- Adequate Intake (AI): Intake at this level is assumed to ensure nutritional adequacy; established when evidence is insufficient to develop an RDA.
- Estimated Average Requirement (EAR): Average daily level of intake estimated to meet the requirements of 50% of healthy individuals; usually used to assess the nutrient intakes of groups of people and to plan nutritionally adequate diets for them; can also be used to assess the nutrient intakes of individuals.
- Tolerable Upper Intake Level (UL): Maximum daily intake unlikely to cause adverse health effects.

Table 1 lists the current RDAs for vitamin B12 [1]. For adults, the main criterion that the FNB used to establish the RDAs was the amount needed to maintain a healthy hematological status and serum vitamin B12 levels. For infants aged 0 to 12 months, the FNB established an AI that is equivalent to the mean intake of vitamin B12 in healthy, breastfed infants.

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

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		
14–18 years	2.4 mcg	2.4 mcg	2.6 mcg	2.8 mcg
19+ years	2.4 mcg	2.4 mcg	2.6 mcg	2.8 mcg

* Adequate Intake (AI)

Sources of Vitamin B12

Food

Vitamin B12 is naturally present in foods of animal origin, including fish, meat, poultry, eggs, and dairy products [5]. In addition, fortified breakfast cereals and fortified nutritional yeasts are readily available sources of vitamin B12 that have high bioavailability [12,13].

The average vitamin B12 level in the breast milk of women with vitamin B12 intakes above the RDA is 0.44 mcg/L [14]. The U.S. Food and Drug Administration specifies that infant formulas sold in the United States must provide at least 0.15 mcg vitamin B12 per 100 kcal [15].

The estimated bioavailability of vitamin B12 from food varies by vitamin B12 dose because absorption decreases drastically when the capacity of intrinsic factor is exceeded (at 1–2 mcg of vitamin B12) [16]. Bioavailability also varies by type of food source. For example, the bioavailability of vitamin B12 appears to be about three times higher in dairy products than in meat, fish, and poultry, and the bioavailability of vitamin B12 from dietary supplements is about 50% higher than that from food sources [17-19].

A variety of foods and their vitamin B12 levels per serving are listed in Table 2.

Table 2: Vitamin B12 Content of Selected Foods [20]

Food	Micrograms per serving	Percent DV*
Beef liver, cooked, pan-fried, 3 ounces	70.7	2,944
Clams (without shells), cooked, 3 ounces	17	708
Tuna, bluefin, cooked, dry heat, 3 ounces	9.3	385
Nutritional yeast, fortified, from several brands (check label), about ¼ cup	8.3 to 24	346 to 1,000
Salmon, Atlantic, cooked, 3 ounces	2.6	108
Beef, ground, 85% lean meat/15% fat, pan-browned, 3 ounces	2.4	100
Milk, 2% milkfat, 1 cup	1.3	54
Yogurt, plain, fat free, 6-ounce container	1.0	43
Breakfast cereals, fortified with 25% of the DV for vitamin B12, 1 serving	0.6	25
Cheese, cheddar, 1½ ounces	0.5	19
Egg, whole, cooked, 1 large	0.5	19
Turkey, breast meat, roasted, 3 ounces	0.3	14
Tempeh, 1/2 cup	0.1	3
Banana, 1 medium	0.0	0
Bread, whole-wheat, 1 slice	0.0	0
Strawberries, raw, halved, 1/2 cup	0.0	0
Beans, kidney, boiled, 1/2 cup	0.0	0
Spinach, boiled, drained, 1/2 cup	0.0	0

*DV = Daily Value. The U.S. Food and Drug Administration (FDA) developed DVs to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin B12 is 2.4 mcg for adults and children aged 4 years and older [21]. FDA does not require food labels to list vitamin B12 content unless vitamin B12 has been added to the food. 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 FoodData Central (https://fdc.nal.usda.gov/) [20] lists the nutrient content of many foods and provides a comprehensive list of foods containing vitamin B12 arranged by nutrient content and by food name.

Dietary supplements

Vitamin B12 is available in multivitamin/mineral supplements, in supplements containing other B-complex vitamins, and in supplements containing only vitamin B12. Multivitamin/mineral supplements typically contain vitamin B12 at doses ranging from 5 to 25 mcg [22]. Vitamin B12 levels are higher, generally 50–500 mcg, in supplements containing vitamin B12 with other B-complex vitamins and even higher, typically 500–1,000 mcg, in supplements containing only vitamin B12.

The most common form of vitamin B12 in dietary supplements is cyanocobalamin [1,3,22,23]. Other forms of vitamin B12 in supplements are adenosylcobalamin, methylcobalamin, and hydroxycobalamin [22].

No evidence indicates that absorption rates of vitamin B12 in supplements vary by form of the vitamin. These rates are about 50% at doses (less than 1–2 mcg) that do not exceed the cobalamin-binding capacity of intrinsic factor and are substantially lower at doses well above 1–2 mcg [23,24]. For example, absorption is only about 2% at doses of 500 mcg and 1.3% at doses of 1,000 mcg [24].

In addition to oral dietary supplements, vitamin B12 is available in sublingual preparations as tablets or lozenges [22]. Evidence suggests no difference in efficacy between oral and sublingual forms [25,26].

Prescription medications

Vitamin B12, in the forms of cyanocobalamin and hydroxycobalamin, can be administered parenterally as a prescription medication, usually by intramuscular injection [2]. Parenteral administration is typically used to treat vitamin B12 deficiency caused by pernicious anemia as well as other conditions (e.g., tropical sprue, pancreatic insufficiency) that result in vitamin B12 malabsorption and severe vitamin B12 deficiency [5].

Vitamin B12 is also available as a prescription nasal gel spray. This formulation appears to be effective in raising vitamin B12 blood levels in adults and children [27,28]. A small clinical study with 10 participants (mean age 81 years) found that the bioavailability of a 1,000 mcg cobalamin dose was 2% with intranasal administration, which is similar to the bioavailability of an oral dose [29].

Vitamin B12 Intakes and Status

Most people in the United States consume adequate amounts of vitamin B12. Data from the 2013–2016 National Health and Nutrition Examination Survey (NHANES) show that only 3% of U.S. men had intakes from food and beverages below the EAR for vitamin B12 of 2 mcg, and the rate for women was 8% [30].

Average daily intakes of vitamin B12 from food are 5.94 mcg for men aged 20 and older and 3.78 mcg for women [31]. For children aged 2–19, mean daily intakes of vitamin B12 from food range from 3.76 mcg to 4.55 mcg [31].

According to an analysis of NHANES data from 2015–2016, people of low socioeconomic status, women, and non-Hispanic Blacks are most likely to have low vitamin B12 intakes [32]. In the United States and the United Kingdom, approximately 6% of adults younger than 60 years have vitamin B12 deficiency, but the rate is closer to 20% in those older than 60 [33]. In addition, serum vitamin B12 levels tend to drop, sometimes to subnormal levels, during pregnancy, but they usually return to normal after delivery [34].

Approximately 24% of men and 29% of women reported using a dietary supplement containing vitamin B12 in NHANES 2017–2018 [31]. The proportion in children ranged from 30% of those aged 2–5 years to 10% of adolescents aged 12–19. Mean vitamin B12 intakes among supplement users from both foods and supplements were 290.3 mcg for men aged 20 and older, 402.5 mcg for women, and from 26.6 to 36.0 mcg for children.

Vitamin B12 Deficiency

Causes of vitamin B12 deficiency include difficulty absorbing vitamin B12 from food, lack of intrinsic factor (e.g., because of pernicious anemia), surgery in the gastrointestinal tract, prolonged use of certain medications (e.g., metformin or proton pump inhibitors, discussed in more detail below in the section on interactions with medications), and dietary deficiency [5,7]. Because people who have difficulty absorbing vitamin B12 from food absorb free vitamin B12 normally, their vitamin B12 deficiency tends to be less severe than that of individuals with pernicious anemia, who cannot absorb either food-bound or free vitamin B12. Certain congenital conditions, such as hereditary intrinsic factor defects and congenital vitamin B12 malabsorption (Imerslund-Gräsbeck disease), can also cause severe vitamin B12 deficiency [5].

The effects of vitamin B12 deficiency can include the hallmark megaloblastic anemia (characterized by large, abnormally nucleated red blood cells) as well as low counts of white and red blood cells, platelets, or a combination; glossitis of the tongue; fatigue; palpitations; pale skin; dementia; weight loss; and infertility [2,5,7]. Neurological changes, such as numbness and tingling in the hands and feet, can also occur [7]. These neurological symptoms can occur without anemia, so early diagnosis and intervention is important to avoid irreversible damage [35]. In pregnant and breastfeeding women, vitamin B12 deficiency might cause neural tube defects, developmental delays, failure to thrive, and anemia in offspring [7].

Because the body stores about 1 to 5 mg vitamin B12 (or about 1,000 to 2,000 times as much as the amount typically consumed in a day), the symptoms of vitamin B12 deficiency can take several years to appear [7,33].

Vitamin B12 deficiency with the classic hematologic and neurologic signs and symptoms is uncommon [11]. However, low or marginal vitamin B12 status (200–300 pg/mL [148–221 pmol/L]) without these symptoms is much more common, at up to 40% in Western populations, especially in those with low intakes of vitamin B12-rich foods [9,11]. The prevalence of vitamin B12 deficiency varies by cutoff level and biomarker used. For example, among adults aged 19 and older who participated in NHANES between 1999 and 2004, the rate of low vitamin B12 levels in serum was 3% with a cutoff of less than 200 pg/mL (148 pmol/L) and 26% with a cutoff of less than 350 pg/mL (258 pmol/L) [36]. Approximately 21% of adults older than 60 had abnormal levels of at least one vitamin B12 biomarker [36].

Typically, vitamin B12 deficiency is treated with vitamin B12 injections, because this method bypasses any barriers to absorption. However, high doses of oral vitamin B12 might also be effective. A 2018 Cochrane review included three randomized controlled trials (RCTs) that compared very high doses (1,000–2,000 mcg) of oral with intramuscular vitamin B12 for vitamin B12 deficiency in a total of 153 participants [37]. The evidence from these studies, although of low quality, showed that the ability of high oral doses of vitamin B12 supplements to normalize serum vitamin B12 was similar to that of intramuscular vitamin B12.

Groups at Risk of Vitamin B12 Inadequacy

The following groups are among those most likely to be vitamin B12 deficient.

Older adults
Depending on the definition used, between 3% and 43% of community-dwelling older adults, especially those with atrophic gastritis, have vitamin B12 deficiency based on serum vitamin B12 levels [38,39]. The deficiency rate at a cutoff of less than 211 mcg/L (156 pmol/L) at admission to a long-term care facility, according to one study, was 14%, and 38% of these older adults had levels lower than 407 pg/mL (300 pmol/L) [39].

Conditions associated with vitamin B12 inadequacy include pernicious anemia, present in about 15% to 25% of older adults with vitamin B12 deficiency [40]. Atrophic gastritis, an autoimmune condition affecting 2% of the general population but 8–9% of adults aged 65 and older, decreases production of intrinsic factor and secretion of hydrochloric acid in the stomach and thus decreases absorption of vitamin B12 [40,41]. A third condition associated with vitamin B12 deficiency in older adults is *Helicobacter pylori* infection, possibly because this bacterium causes inflammation that leads to malabsorption of vitamin B12 from food [42].

Individuals with pernicious anemia
Pernicious anemia is an irreversible autoimmune disease that affects the gastric mucosa and results in gastric atrophy [1,43]. This disease leads to attacks on parietal cells in the stomach, resulting in failure to produce intrinsic factor and malabsorption of dietary vitamin B12, recycled biliary vitamin B12, and free vitamin B12 [1,6,11].Therefore, without treatment, pernicious anemia causes vitamin B12 deficiency, even in the presence of adequate vitamin B12 intakes.

Pernicious anemia is the most common cause of clinically evident vitamin B12 deficiency around the world [11,43]. The incidence of pernicious anemia in the United States is an estimated 151 per

100,000, and this condition is more common in women and in people of European ancestry [43].

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 [2,3,44]. But although rates of vitamin B12 deficiency are higher in people with celiac disease than other people [45], the evidence for whether rates of vitamin B12 deficiency are higher in people with Crohn's disease is mixed [44,46,47]. Vitamin B12 deficiency in people with Crohn's disease is typically treated with intramuscular cobalamin injections, but high doses of oral cyanocobalamin therapy (e.g., 1,000 mcg/day) might be equally effective [48].

Individuals who have had gastrointestinal surgery

Surgical procedures in the gastrointestinal tract, such as for weight loss or to remove all or part of the stomach, can cause a complete or partial loss of cells that secrete hydrochloric acid and cells that secrete intrinsic factor [49,50]. Thus, these procedures reduce the amount of vitamin B12, particularly food-bound vitamin B12, that the body absorbs [49,50]. High doses (1,000 mcg/day) of oral methylcobalamin supplements appear to be as effective as hydroxycobalamin injections in normalizing vitamin B12 values in patients who have undergone Roux-en-Y gastric bypass surgery [51].

Vegetarians

Vegans who consume no animal products and vegetarians who consume some animal products (e.g., dairy products, eggs, or both) but not meat have a higher risk of developing vitamin B12 deficiency because natural food sources of vitamin B12 are limited to animal foods [3,52]. Consumption of foods fortified with vitamin B12 (such as fortified nutritional yeasts) as well as vitamin B12 supplements can substantially reduce the risk of deficiency [52].

Infants of vegan women

Exclusively breastfed infants of women who consume no animal products might have very limited reserves of vitamin B12 and can develop vitamin B12 deficiency, sometimes very early in life [53]. The infant's deficiency can be severe, especially if the mother's deficiency is severe or caused by pernicious anemia; sometimes, the mother's own deficiency is clinically mild and not recognized. Undetected and untreated vitamin B12 deficiency in infants can result in neurological damage, failure to thrive, developmental delays, and anemia [2,53,54]. The reasons include the small amounts of vitamin B12 in the breast milk of vegan mothers as well as the limited amounts of vitamin B12 crossing the placenta in these women during fetal development.

Vitamin B12 and Health

This section focuses on areas of health in which vitamin B12 might be involved: cancer, cardiovascular disease (CVD) and stroke, dementia and cognitive function, and energy and endurance.

Cancer

The evidence for a relationship between vitamin B12 and cancer risk is mixed. Some evidence supports a link between increased cancer risk and higher intakes or blood concentrations of vitamin

B12, some supports a link with lower intakes or concentrations, and some evidence indicates no link at all.

Observational evidence supporting an association between higher vitamin B12 levels and increased cancer risk includes an analysis of data on 757,185 people (median age 56 years) with plasma vitamin B12 measurements [55]. The results showed that the adjusted 1-year risk of cancer was 1.74 to 4.72 times higher among those with vitamin B12 levels above 813 pg/mL (600 pmol/L) than those with levels in the normal range of 203–813 pg/mL (150–600 pmol/L). An analysis by some of the same investigators of data from Danish medical registries for 25,017 people who had a cancer diagnosis between 1998 and 2014 found 1-year survival rates of 35.8% in those whose plasma cobalamin levels were higher than 1,084 pg/mL (800 pmol/L) and 69.3% in those with levels between 271 and 813 pg/mL (200–600 pmol/L) [56].

Some observational evidence also shows an association between supplements containing vitamin B12 and a higher risk of certain types of cancer. For example, an assessment of 77,118 participants aged 50 to 76 years in the Vitamins and Lifestyle cohort study found that use of at least 55 mcg/day supplemental vitamin B12 for an average of 10 years was associated with a 40% higher risk of lung cancer in men [57]. However, the study found no association between supplemental vitamin B12 use and cancer risk in women.

Limited clinical trial evidence supports the finding that higher vitamin B12 intakes might increase cancer risk. In an analysis of data on 2,524 participants in the B Vitamins for the Prevention of Osteoporotic Fractures trial who were treated with supplements containing 400 mcg/day folic acid and 500 mcg/day vitamin B12 for 2 to 3 years, the risk of colorectal cancer was significantly higher, at 3.4%, in the supplementation group than in the placebo group, whose rate was 2% [58]. However, high folic acid levels are potentially linked to increased risk of colorectal cancer, so the result might be due to the folic acid rather than the vitamin B12 [59]. Furthermore, the supplements had no significant effect on overall cancer risk.

Some observational evidence shows no association between high vitamin B12 concentrations or intakes and increased risk of certain cancers. For example, higher vitamin B12 intakes or serum concentrations were not associated with an increased risk of pancreatic cancer [60], breast cancer [61], or esophageal cancer or gastric cancer [62]. Clinical trials support the lack of association between higher vitamin B12 intakes and cancer risk. [63-65]. For example, a meta-analysis of 18 RCTs that included 74,498 individuals found that supplements containing B vitamins, including 20 to 2,000 mcg/day vitamin B12, had little or no effect on cancer incidence, cancer deaths, or all-cause mortality during follow-up periods of 2 to 7.3 years [65].

Finally, evidence pointing to an association between lower vitamin B12 levels and a higher cancer risk includes observational data showing a risk of gastric cancer that was 5.8 times higher in male smokers with lower vitamin B12 levels (less than 394 pg/mL [291 pmol/L]) than in those with levels higher than 591 pg/mL (436 pmol/L) [66]. Also, two meta-analyses found associations between lower vitamin B12 concentrations or intakes and a higher risk of colorectal cancer [67] and prostate cancer [68].

More evidence is needed to clarify whether high or low intakes of vitamin B12 influence the risk of cancer as well as the role of vitamin B12 in preventing cancer.

Cardiovascular disease and stroke

An elevated homocysteine level has been associated with an increased risk of CVD [69,70]. Vitamin B12 and other B vitamins are involved in homocysteine metabolism, and researchers have hypothesized that supplementation with these micronutrients can reduce CVD risk by lowering homocysteine levels [69,70].

However, studies on the association between vitamin B12 intake and risk of CVD have had negative results. Two meta-analyses—one of 11 prospective cohort studies in 369,746 individuals who developed 5,133 cases of coronary heart disease and one of 12 prospective (mostly cohort) studies in 389,938 participants who developed 10,749 cases of stroke over 4.2 to 19 years (including 10 reports that evaluated the association between dietary vitamin B12 intake and stroke risk)−−found no significant association between vitamin B12 intakes and risk of coronary heart disease [71] or stroke [72].

RCTs have found that vitamin B12 (and folic acid) supplements lower homocysteine levels, but not CVD risk. The authors of a Cochrane review of the effects of homocysteine-lowering interventions on cardiovascular events based on 15 studies in 71,422 participants concluded that supplements of vitamin B12 alone or with other B vitamins do not prevent heart attacks or reduce death rates in people at risk of or with CVD [73]. More recently, an extended follow-up of the B-PROOF trial, (which compared 400 mcg folic acid and 500 mcg vitamin B-12 daily with placebo) in 1,298 participants found that after a median of 54 months, the intervention had no effect on CVD risk [74].

Overall, the available evidence suggests that supplementation with vitamin B12 alone or in combination with other B-vitamins does not reduce the risk of CVD or of CVD-related death.

Dementia and cognitive function

Observational studies have shown positive associations between elevated homocysteine levels and the incidence of both Alzheimer's disease and dementia [75-78]. Scientists hypothesize that elevated homocysteine levels might have a negative effect on the brain via numerous mechanisms, including cerebrovascular ischemia leading to neuronal cell death, activation of tau kinases leading to tangle deposition, and inhibition of methylation reactions [77].

Most observational studies have found correlations between low serum vitamin B12 concentrations alone or in combination with high folate concentrations and poor cognitive function [79-84]. For example, an analysis of cross-sectional 2011–2014 NHANES data on 2,420 adults aged 60 years or older found that low vitamin B12 (MMA greater than 0.27 micromol/L or serum vitamin B12 less than 203 pg/mL [150 pmol/L]) combined with high folic acid—unmetabolized serum folic acid greater than 0.44 mcg/L (1 nmol/L) or serum total folate higher than 32.7 mcg/L (74.1 nmol/L)—was associated an almost two to three times higher risk of cognitive impairment [79].

However, a few observational studies have found no such association [85,86]. In addition, according to a systematic review of 35 prospective cohort studies in 14,325 participants aged 47 to 101 years followed for an average of 5.4 years, the evidence does not support a role for low vitamin B12 in the development of cognitive impairment or dementia [87].

In general, evidence from RCTs does not show that vitamin B12 supplementation alone or with folic acid, vitamin B6, or both for 1 to 2 years improves cognitive function in older adults with or without dementia, mild cognitive impairment, or Alzheimer's disease, even though supplementation lowers homocysteine levels [88-91]. For example, an RCT administered 400 mcg/day folic acid and 500 mcg/day vitamin B12 (B-vitamin group) or a placebo for 2 years to 2,919 adults aged 65 and older with homocysteine levels of 12 to 50 mcmol/L [90]. Although homocysteine concentrations declined significantly more (by 5.0 mcmol/L) in the supplementation group than in the placebo group (1.3 mcmol/L), cognitive test scores did not differ between groups. A Cochrane review of vitamin and mineral supplements to maintain cognitive function in cognitively healthy people included 14 studies that compared folic acid, vitamin B12, vitamin B6, or a combination of these supplements to placebo in 27,882 participants, most of whom were aged 60 years or older [92]. The supplements had little to no effect on global cognitive function when administered for up to 5 years and also appeared to have no impact when administered for 5 to 10 years.

Similarly, supplementation with vitamin B12 alone or with other B vitamins does not appear to decrease the risk or slow the progression of dementia or Alzheimer's disease in older adults. A Cochrane review evaluated the effects of vitamin and mineral supplements on cognitive function and dementia in people with mild cognitive impairment [93]. The review included 5 trials with 879 participants that investigated B vitamin supplements (one study of folic acid only, and four trials of vitamins B6 and B12 and folic acid). Taking these B vitamins for 6 to 24 months had no apparent effect on episodic memory, executive function, speed of processing, or quality of life, although one study found a slower rate of brain atrophy over 2 years.

Additional clinical trials are needed to better understand the effects of vitamin B12 supplementation on cognitive function and cognitive decline.

Energy and endurance
Because of its role in energy metabolism, vitamin B12 is often promoted as an energy enhancer and an athletic performance and endurance booster. However, vitamin B12 supplementation appears to have no beneficial effect on performance in the absence of a nutritional deficit [94,95].

Health Risks from Excessive Vitamin B12

The FNB did not establish a UL for vitamin B12 because of its low potential for toxicity [1]. Even at large doses, vitamin B12 is generally considered to be safe because the body does not store excess amounts.

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.

Gastric acid inhibitors
Gastric acid inhibitors include proton pump inhibitors, such as omeprazole (Prilosec®) and lansoprazole (Prevacid®), and histamine 2-receptor antagonists, such as cimetidine (Tagamet®) and ranitidine (Zantac®). These drugs are used to treat gastroesophageal reflux disease and peptic ulcer disease. They can interfere with vitamin B12 absorption from food by slowing the release of gastric acid into the stomach and thereby lead to vitamin B12 deficiency [96-98].

Metformin
Metformin, an antihyperglycemic agent used as first-line treatment for prediabetes and diabetes, might reduce the absorption of vitamin B12 and significantly reduce serum vitamin B12 concentrations [98].

Vitamin B12 and Healthful Diets

The federal government's 2020-2025 Dietary Guidelines for Americans notes that "Because foods provide an array of nutrients and other components that have benefits for health, nutritional needs should be met primarily through foods. … In some cases, fortified foods and dietary supplements are useful when it is not possible otherwise to meet needs for one or more nutrients (e.g., during specific life stages such as pregnancy)."

For more information about building a healthy dietary pattern, refer to the *Dietary Guidelines for Americans (https://www.dietaryguidelines.gov)* and the U.S. Department of Agriculture's *MyPlate. (https://www.choosemyplate.gov/)*

The *Dietary Guidelines for Americans* describes a healthy dietary pattern as one that:

- Includes a variety of vegetables; fruits; grains (at least half whole grains); fat-free and low-fat milk, yogurt, and cheese; and oils.
  Milk and milk products are good sources of vitamin B12. Many ready-to-eat breakfast cereals are fortified with vitamin B12.
- Includes a variety of protein foods such as lean meats; poultry; eggs; seafood; beans, peas, and lentils; nuts and seeds; and soy products.
  Fish and red meat are excellent sources of vitamin B12. Poultry and eggs also contain vitamin B12.
- Limits foods and beverages higher in added sugars, saturated fat, and sodium.
- Limits alcoholic beverages.
- Stays within your daily calorie needs.

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