Folate

Dietary Supplement Fact Sheet

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Introduction

Folate is a water-soluble B vitamin that is naturally present in some foods, added to others, and available as a dietary supplement. Folate, formerly known as folacin, is the generic term for both naturally occurring food folate and folic acid, the fully oxidized monoglutamate form of the vitamin that is used in dietary supplements and fortified foods. Folic acid consists of a p-aminobenzoic molecule linked to a pteridine ring and one molecule of glutamic acid. Food folates, which exist in various forms, contain additional glutamate residues, making them polyglutamates [1].

Folate functions as a coenzyme or cosubstrate in single-carbon transfers in the synthesis of nucleic acids (DNA and RNA) and metabolism of amino acids [1-3]. One of the most important folate-dependent reactions is the conversion of homocysteine to methionine in the synthesis of S-adenosyl-methionine, an important methyl donor [1-3]. Another folate-dependent reaction, the methylation of deoxyuridylate to thymidylate in the formation of DNA, is required for proper cell division. An impairment of this reaction initiates a process that can lead to megaloblastic anemia, one of the hallmarks of folate deficiency [3].

When consumed, food folates are hydrolyzed to the monoglutamate form in the gut prior to absorption by active transport across the intestinal mucosa [2]. Passive diffusion also occurs when pharmacological doses of folic acid are consumed [2]. Before entering the bloodstream, the monoglutamate form is reduced to tetrahydrofolate (THF) and converted to either methyl or formyl forms [1]. The main form of folate in plasma is 5-methyl-THF. Folic acid can also be found in the blood unaltered (known as unmetabolized folic acid), but whether this form has any biological activity or can be used as a biomarker of status is not known [4].

The total body content of folate is estimated to be 10 to 30 mg; about half of this amount is stored in the liver [1,3] and the remainder in blood and body tissues. A serum folate concentration is commonly used to assess folate status, with a value above 3 nanograms (ng)/mL indicating adequacy [1,2]. This indicator, however, is sensitive to recent dietary intake, so it might not reflect long-term status. Erythrocyte folate concentration provides a longer-term measure of folate intakes, so when day-to-day folate intakes are variable—such as in people who are ill and whose folate intake has recently declined—it might be a better indicator of tissue folate stores than serum folate concentration [2,4]. An erythrocyte folate concentration above 140 ng/mL indicates adequate folate status [2,4], although some researchers have suggested that higher values are optimal for preventing neural tube defects [5].

A combination of serum or erythrocyte concentration and indicators of metabolic function can also be used to assess folate status. Plasma homocysteine concentration is a commonly used functional indicator of folate status because homocysteine levels rise when the body cannot convert homocysteine to methionine due to a 5-methyl-THF deficiency. Homocysteine levels, however, are not a highly specific indicator of folate status because they can be influenced by other factors, including kidney dysfunction and deficiencies of vitamin B12 and other micronutrients [1,3,6]. The most commonly used cutoff value for elevated homocysteine is 16 micromoles/L, although slightly lower values of 12 to 14 micromoles/L have also been used [2].

Recommended Intakes

Intake recommendations for folate 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) [2]. 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, 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 folate as micrograms (mcg) of dietary folate equivalents (DFEs). The FNB developed DFEs to reflect the higher bioavailability of folic acid than that of food folate. At least 85% of folic acid is estimated to be bioavailable when taken with food, whereas only about 50% of folate naturally present in food is bioavailable [2,3]. Based on these values, the FNB defined DFE as follows:

- 1 mcg DFE = 1 mcg food folate
- 1 mcg DFE = 0.6 mcg folic acid from fortified foods or dietary supplements consumed with foods

- 1 mcg DFE = 0.5 mcg folic acid from dietary supplements taken on an empty stomach

For infants from birth to 12 months, the FNB established an AI for folate that is equivalent to the mean intake of folate in healthy, breastfed infants in the United States.

Table 1: Recommended Dietary Allowances (RDAs) for Folate [2]

Age	Male	Female	Pregnant	Lactating
Birth to 6 months*	65 mcg DFE*	65 mcg DFE*		
7–12 months*	80 mcg DFE*	80 mcg DFE*		
1–3 years	150 mcg DFE	150 mcg DFE		
4–8 years	200 mcg DFE	200 mcg DFE		
9–13 years	300 mcg DFE	300 mcg DFE		
14–18 years	400 mcg DFE	400 mcg DFE	600 mcg DFE	500 mcg DFE
19+ years	400 mcg DFE	400 mcg DFE	600 mcg DFE	500 mcg DFE

* Adequate Intake (AI)

Sources of Folate

Food

Folate is found naturally in a wide variety of foods, including vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, dairy products, poultry and meat, eggs, seafood, and grains (Table 2) [3,7]. Spinach, liver, yeast, asparagus, and Brussels sprouts are among the foods with the highest levels of folate.

In January 1998, the U.S. Food and Drug Administration (FDA) began requiring manufacturers to add folic acid to enriched breads, cereals, flours, cornmeals, pastas, rice, and other grain products [8]. Because cereals and grains are widely consumed in the United States, these products have become very important contributors of folic acid to the American diet. The fortification program was projected to increase folic acid intakes by approximately 100 mcg/day [9,10], but the program actually increased mean folic acid intakes in the United States by about 190 mcg/day [10]. In April 2016, FDA approved the voluntary addition of folic acid to corn masa flour at levels consistent with other enriched grain products [11].

The Canadian government has also required the addition of folic acid to many grains, including white flour, enriched pasta, and cornmeal, since November 1, 1998 [12-14]. Other countries, including Costa Rica, Chile, and South Africa, have also established mandatory folic acid fortification programs [15].

Table 2: Selected Food Sources of Folate and Folic Acid [7]

Food	mcg DFE per serving	Percent DV*
Beef liver, braised, 3 ounces	215	54
Spinach, boiled, ½ cup	131	33
Black-eyed peas (cowpeas), boiled, ½ cup	105	26
Breakfast cereals, fortified with 25% of the DV†	100	25
Rice, white, medium-grain, cooked, ½ cup†	90	23
Asparagus, boiled, 4 spears	89	22
Spaghetti, cooked, enriched, ½ cup†	83	21
Brussels sprouts, frozen, boiled, ½ cup	78	20
Lettuce, romaine, shredded, 1 cup	64	16

Food	mcg DFE per serving	Percent DV*
Avocado, raw, sliced, ½ cup	59	15
Spinach, raw, 1 cup	58	15
Broccoli, chopped, frozen, cooked, ½ cup	52	13
Mustard greens, chopped, frozen, boiled, ½ cup	52	13
Green peas, frozen, boiled, ½ cup	47	12
Kidney beans, canned, ½ cup	46	12
Bread, white, 1 slice†	43	11
Peanuts, dry roasted, 1 ounce	41	10
Wheat germ, 2 tablespoons	40	10
Tomato juice, canned, ¾ cup	36	9
Crab, Dungeness, 3 ounces	36	9
Orange juice, ¾ cup	35	9
Turnip greens, frozen, boiled, ½ cup	32	8
Orange, fresh, 1 small	29	7
Papaya, raw, cubed, ½ cup	27	7
Banana, 1 medium	24	6
Yeast, baker's, ¼ teaspoon	23	6
Egg, whole, hard-boiled, 1 large	22	6
Vegetarian baked beans, canned, ½ cup	15	4
Cantaloupe, raw, 1 wedge	14	4
Fish, halibut, cooked, 3 ounces	12	3
Milk, 1% fat, 1 cup	12	3
Ground beef, 85% lean, cooked, 3 ounces	7	2
Chicken breast, roasted, ½ breast	3	1

* DV = Daily Value. The FDA developed DVs to help consumers compare the nutrient contents of products within the context of a total diet. The DV for folate is 400 mcg for adults and children aged 4 and older. However, the FDA does not require food labels to list folate 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.

† Fortified with folic acid as part of the folate fortification program.

The U.S. Department of Agriculture's Nutrient Database Web site [7] lists the nutrient content of many foods and provides a comprehensive list of foods containing folate arranged by nutrient content and by food name.

Dietary supplements

Folic acid is available in multivitamins (frequently at a dose of 400 mcg) and prenatal vitamins, in supplements containing other B-complex vitamins, and as a stand-alone supplement. Children's multivitamins commonly contain between 200 and 400 mcg folic acid [16]. About 85% of supplemental folic acid, when taken with food, is bioavailable [2,3]. When consumed without food, nearly 100% of supplemental folic acid is bioavailable [2,3].

About 35% of adults and 28% of children aged 1 to 13 years in the United States use supplements containing folic acid [17,18]. Adults aged 51 to 70 years are more likely than members of other age groups to take supplements containing folic acid. Use is also higher among non-Hispanic whites than non-Hispanic blacks or Mexican Americans [17,18].

Folate Intakes and Status

According to analyses of data from the 2003–2006 National Health and Nutrition Examination Survey (NHANES), most people in the United States obtain adequate amounts of folate, although some groups are still at risk of obtaining insufficient amounts. Mean dietary intakes of folate (including food folate and folic acid from fortified foods) range from 454 to 652 mcg DFE per day in U.S. adults of various ages and from 385 to 674 mcg DFE in children aged 1 to 18 years [17,18].

Measurements of erythrocyte folate levels also suggest that most people in the United States have adequate folate status. According to an analysis of NHANES 2003–2006 data, less than 0.5% of children aged 1 to 18 years have deficient erythrocyte folate concentrations [16]. Mean concentrations in this age group range from 211 to 294 ng/mL depending on age, dietary habits, and supplement use. In adults, mean erythrocyte folate concentrations range from 216 to 398 ng/mL, also indicating adequate folate status [19].

However, certain groups, including women of childbearing age and non-Hispanic black women, are at risk of insufficient folate intakes. Even when intake of folic acid from dietary supplements is included, 19% of female adolescents aged 14 to 18 years and 17% of women aged 19 to 30 years do not meet the EAR [17]. Similarly, 23% of non-Hispanic black women have inadequate total intakes, compared with 13% of non-Hispanic white women.

Some population groups are at risk of obtaining excessive folate. People aged 50 years and older have the highest total folate intakes and about 5% have intakes exceeding the UL of 1,000 mcg per day, primarily due to folic acid from dietary supplements [17]. Many children's intakes also exceed the UL. When folic acid from both food and dietary supplements is considered, 30% to 66% of children aged 1 to 13 years have intakes exceeding the UL of 300–600 mcg per day depending on age [18]. Almost all children aged 1 to 8 years who consume at least 200 mcg/day folic acid from dietary supplements have total folate intakes that exceed the UL [16]. However, it is not clear whether this is of concern because little is known about the long-term effects of high folic acid doses in children [4].

Folate Deficiency

Isolated folate deficiency is uncommon; it usually coexists with other nutrient deficiencies because of its strong association with poor diet, alcoholism, and, sometimes, malabsorptive disorders [3]. Megaloblastic anemia, which is characterized by large, abnormally nucleated erythrocytes, is the primary clinical sign of a deficiency of folate or vitamin B12 [1,3]. Symptoms of megaloblastic anemia include weakness, fatigue, difficulty concentrating, irritability, headache, heart palpitations, and shortness of breath [2].

Folate deficiency can also produce soreness and shallow ulcerations in the tongue and oral mucosa; changes in skin, hair, or fingernail pigmentation; and elevated blood concentrations of homocysteine [1-3,20].

Women with insufficient folate intakes are at increased risk of giving birth to infants with neural tube defects (NTDs) although the mechanism responsible for this effect is unknown [2]. Inadequate maternal folate status has also been associated with low infant birth weight, preterm delivery, and fetal growth retardation [21].

Groups at Risk of Folate Inadequacy

Frank folate deficiency is rare in the United States, but some individuals might have marginal folate status. The following groups are among those most likely to be at risk of folate inadequacy.

People with alcohol dependence

People with alcohol dependence frequently have poor-quality diets that contain insufficient amounts of folate. Moreover, alcohol interferes with folate absorption and metabolism and accelerates its breakdown [1,3]. An evaluation of the nutritional status of people with chronic alcoholism in Portugal, where the food supply is not fortified with folic acid, found low folate status in more than 60% of those studied [22]. Even moderate alcohol consumption of 240 ml (8 fluid ounces) red wine per day or 80 ml (2.7 fluid ounces) vodka per day for 2 weeks can significantly decrease serum folate concentrations in healthy men, although not below the cutoff level for folate adequacy of 3 ng/ml [23].

Women of childbearing age

All women capable of becoming pregnant should obtain adequate amounts of folate to reduce the risk of NTDs and other birth defects. Unfortunately, some women of childbearing age obtain insufficient folate even when intakes from both food and dietary supplements are included [17]. Women of childbearing age should obtain 400 mcg/day of folic acid from dietary supplements and/or fortified foods in addition to the folate present in a varied diet [2].

Pregnant women

During pregnancy, demands for folate increase due to its role in nucleic acid synthesis [21]. To accommodate this need, the FNB increased the folate RDA from 400 mcg/day for nonpregnant women to 600 mcg/day during pregnancy [2]. This level of intake might be difficult for many women to achieve through diet alone. The American College of Obstetricians and Gynecologists recommends a prenatal vitamin supplement for most pregnant women to ensure that they obtain adequate amounts of folic acid and other nutrients [24].

People with malabsorptive disorders

Several medical conditions increase the risk of folate deficiency. People with malabsorptive disorders—including tropical sprue, celiac disease, and inflammatory bowel disease—might have lower folate absorption than people without these disorders [3]. Diminished gastric acid secretion associated with atrophic gastritis, gastric surgery, and other conditions can also reduce folate absorption [3].

Folate and Health

Cancer

Several epidemiological studies have suggested an inverse association between folate status and the risk of colorectal, lung, pancreatic, esophageal, stomach, cervical, ovarian, breast, and other cancers [1,25]. Folate might influence the development of cancer through its role in one-carbon metabolism and subsequent effects on DNA replication and cell division [25,26]. However, research has not established the precise nature of folate's effect on carcinogenesis.

Results from clinical trials involving folic acid supplementation have been mixed. For example, in the Supplementation with Folate, Vitamins B6 and B12 and/or Omega-3 Fatty Acids trial conducted in France, in which 2,501 people with a history of cardiovascular disease received daily supplements of 560 mcg folic acid, 3 mg vitamin B6, and 20 mcg vitamin B12 for 5 years, researchers found no association between B-vitamin supplementation and cancer outcomes [27]. In a combined analysis of two trials conducted in Norway (where foods are not fortified with folic acid), supplementation with folic acid (800 mcg/day) plus vitamin B12 (400 mcg/day) for a median of 39 months in 3,411 people with ischemic heart disease increased cancer incidence by 21% and cancer mortality by 38% compared with no supplementation [28]. Findings from these Norwegian trials have raised concerns about the potential of folic acid supplementation to raise cancer risk.

The most thorough research has focused on folate's effect on the development of colorectal cancer and its precursor, adenoma [1,25]. Several epidemiological studies have found inverse associations between high dietary folate intake and the risk of colorectal adenoma and colorectal cancer [29-31]. For example, in the NIH-AARP Diet and Health Study, a cohort study of more than 525,000 people aged 50 to 71 years in the United States, individuals with total folate intakes of 900 mcg/day or higher had a 30% lower risk of colorectal cancer than those with intakes less than 200 mcg/day [31].

Several clinical trials have examined whether supplemental folic acid reduces the risk of colorectal adenoma in individuals with or without a history of adenoma. In the Women's Antioxidant and Folic Acid Cardiovascular Study, which included 1,470 older women at high risk of cardiovascular disease, daily supplementation with 2,500 mcg folic acid, 50 mg vitamin B6, and 1,000 mcg vitamin B12 did not affect the occurrence of colorectal adenoma during 7.3 years of intervention and about 2 years of postintervention follow-up [32]. A pooled analysis of three large clinical trials (one conducted in Canada, one in both the United States and Canada, and one in both the United Kingdom and Denmark) found that folic acid supplementation for up to 3.5 years neither increased nor decreased the recurrence of adenomas in people with a history of adenoma [33]. Folic acid supplementation also had no effect on the risk of all cancer types combined. However, in one of the studies included in the analysis, folic acid supplementation (1,000 mcg/day) significantly increased the risk of having three or more adenomas and the risk of noncolorectal cancers (although it had no effect on the risk of colorectal cancer) [34]. A secondary analysis of this study found that folic acid supplementation significantly increased the risk of prostate cancer [35]. Subsequent research has shown an association between increased cancer cell proliferation and higher serum folate concentrations in men with prostate cancer [36].

These findings, combined with evidence from laboratory and animal studies indicating that high folate status promotes tumor progression, suggest that folate might play dual roles in the risk of colorectal cancer, and possibly other cancers, depending on the dosage and timing of the exposure. Modest doses of folic acid taken before preneoplastic lesions are established might suppress the development of cancer in normal tissues, whereas high doses taken after the establishment of preneoplastic lesions might promote cancer development and progression [37-39]. This hypothesis is supported by a 2011 prospective study that found an inverse association between folate intake and risk of colorectal cancer only during early preadenoma stages [40].

Additional research is needed to fully understand the role of dietary folate and supplemental folic acid in colorectal, prostate, and other cancers. Evidence to date indicates that adequate folate intake might reduce the risk of some forms of cancer. However, high doses of supplemental folic acid should be used with caution, especially by individuals with a history of colorectal adenomas.

Cardiovascular disease and stroke

An elevated homocysteine level has been associated with an increased risk of cardiovascular disease [1,2]. Folate and other B vitamins are involved in homocysteine metabolism and researchers have hypothesized that they reduce cardiovascular disease risk by lowering homocysteine levels [41].

Although folic acid (and vitamin B12) supplements lower homocysteine levels, research indicates that these supplements do not actually decrease the risk of cardiovascular disease, although they might provide protection from stroke [41-47]. The Heart Outcomes Prevention Evaluation (HOPE) 2 study, for example, recruited 5,522 patients aged 55 years or older with vascular disease or diabetes from some countries—including the United States and Canada—that had a folic acid fortification program and some countries that did not [44]. Patients received 2,500 mcg folic acid plus 50 mg vitamin B6 and 1 mg vitamin B12 or placebo for an average of 5 years. Compared with placebo, treatment with B vitamins significantly decreased homocysteine levels but did not reduce the risk of death from cardiovascular causes or myocardial infarction. Supplementation did, however, significantly

reduce the risk of stroke. In the Women's Antioxidant and Folic Acid Cardiovascular Study, U.S. women at high risk of cardiovascular disease who took daily supplements containing 2,500 mcg folic acid, 1 mg vitamin B12, and 50 mg vitamin B6 for 7.3 years did not have a reduced risk of major cardiovascular events, even though the supplements lowered their homocysteine levels [45].

The authors of a 2012 meta-analysis of 19 randomized controlled trials that included 47,921 participants concluded that B-vitamin supplementation has no effect on the risk of cardiovascular disease, myocardial infarction, coronary heart disease, or cardiovascular death, although it does reduce the risk of stroke by 12% [42]. It is not possible to evaluate the impact of folic acid alone from these trials, but little evidence shows that supplemental folic acid with or without vitamin B12 and vitamin B6 can help reduce the risk or severity of cardiovascular disease [42,48]. B-vitamin supplementation does, however, appear to have a protective effect on stroke [421].

Dementia, cognitive function, and Alzheimer's disease

Most observational studies show positive associations between elevated homocysteine levels and the incidence of both Alzheimer's disease and dementia [20,49-51]. Some, but not all, observational studies have also found correlations between low serum folate concentrations and both poor cognitive function and higher risk of dementia and Alzheimer's disease [49,50,52].

Despite this evidence, most research has not shown that folic acid supplementation affects cognitive function or the development of dementia or Alzheimer's disease. In one randomized, double-blind, placebo-controlled trial conducted in the Netherlands, 195 people aged 70 years or older with no or moderate cognitive impairment received one of three treatments for 24 weeks: 400 mcg folic acid plus 1 mg vitamin B12; 1 mg vitamin B12; or placebo [53]. Treatment with folic acid plus vitamin B12 reduced homocysteine concentrations by 36% but did not improve cognitive function.

As part of the Women's Antioxidant and Folic Acid Cardiovascular Study, 2,009 U.S. women aged 65 years or older at high risk of cardiovascular disease were randomly assigned to receive daily supplements containing 2,500 mcg folic acid plus 1 mg vitamin B12 and 50 mg vitamin B6 or placebo [54]. After an average 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 a low baseline dietary intake of B vitamins, supplementation significantly slowed the rate of cognitive decline. In a trial that included 340 individuals in the United States with mild-to-moderate Alzheimer's disease, daily supplements of 5,000 mcg folic acid plus 1 mg vitamin B12 and 25 mg vitamin B6 for 18 months did not slow cognitive decline compared with placebo [55].

A secondary analysis of a study conducted in Australia (which did not have mandatory folic acid fortification at the time) found that daily supplementation with 400 mcg folic acid plus 100 mcg vitamin B12 for 2 years improved some measures of cognitive function, particularly memory, in 900 adults aged 60 to 74 years who had depressive symptoms [56].

Several large reviews have evaluated the effect of B vitamins on cognitive function [57-60]. Although additional research is still needed, evidence to date indicates that supplementation with folic acid alone or in combination with vitamin B12 or vitamin B6 does not appear to improve cognitive function in individuals with or without existing cognitive impairment [57-60].

Depression

Low folate status has been linked to depression and poor response to antidepressants [61-63]. In an ethnically diverse population study of 2,948 people aged 1 to 39 years in the United States, serum and erythrocyte folate concentrations were significantly lower in individuals with major depression than in those who had never been

depressed [62]. Results from a study of 52 men and women with major depressive disorder showed that only 1 of 14 subjects with low serum folate levels responded to antidepressant treatment compared with 17 of 38 subjects with normal folate levels [64].

Although supplemental folic acid has not been proposed as a replacement for traditional antidepressant therapy, it might be helpful as an adjuvant treatment [63,65]. In a trial conducted in the United Kingdom, 127 patients with major depression were randomly assigned to receive either 500 mcg folic acid or placebo in addition to 20 mg of fluoxetine (an antidepressant medication) daily for 10 weeks [61]. Although the effects in men were not statistically significant, women who received fluoxetine plus folic acid had a significantly greater improvement in depressive symptoms than those who received fluoxetine plus placebo. The authors of a Cochrane review of folate for depressive disorders concluded that folate "may have a potential role as a supplement to other treatment for depression," although whether this applies to both people with normal folate levels and those with folate deficiency is unclear [65]. Additional research is needed to fully understand the association between folate status and depression and whether folic acid supplementation might be a helpful adjuvant treatment.

Neural tube defects

NTDs result in malformations of the spine (spina bifida), skull, and brain (anencephaly). They are the most common major congenital malformations of the central nervous system and result from a failure of the neural tube to close at either the upper or lower end during days 21 to 28 after conception [14,66]. The incidence of NTDs varies from 0.5 to 4.0 per 1,000 births in North America [14]. Rates of spina bifida and anencephaly (the two most common types of NTDs) are highest among Hispanic women and lowest among African American and Asian women [13].

Due to its role in the synthesis of DNA and other critical cell components, folate is especially important during phases of rapid cell growth [67]. Clear clinical trial evidence shows that when women take folic acid periconceptionally, a substantial proportion of NTDs is prevented [14,38,66,68,69]. Scientists estimate that periconceptional folic acid use could reduce NTDs by 50% to 60% [66].

Since 1998, when the mandatory folic acid fortification program took effect in the United States, NTD rates have declined by 25% to 30% [66]. However, significant racial and ethnic disparities exist. Spina bifida and anencephaly rates have declined significantly among Hispanic and non-Hispanic white births in the United States, but not among non-Hispanic black births [70]. Differences in dietary habits and supplement-taking practices could be a factor in these disparities [70]. In addition, factors other than folate status—such as maternal diabetes, obesity, and intake of other nutrients such as vitamin B12—are believed to affect the risk of NTDs [13,14,69,71,72].

Because approximately 50% of pregnancies in the United States are unplanned, adequate folate status is especially important during the periconceptual period before a woman might be aware that she is pregnant. The FNB advises women capable of becoming pregnant to "consume 400 mcg of folate daily from supplements, fortified foods, or both in addition to consuming food folate from a varied diet" [2]. The U.S. Public Health Service and the Centers for Disease Control and Prevention have published similar recommendations [73].

The FNB has not issued recommendations for women who have had a previous NTD and are planning to become pregnant again. However, other experts recommend that women obtain 4,000 to 5,000 mcg supplemental folic acid daily starting at least 1 to 3 months prior to conception and continuing for 2½ to 3 months after conception [14,74]. These doses exceed the UL and should be taken only under the supervision of a physician [74].

Preterm birth, congenital heart defects, and other congenital anomalies

Folic acid supplementation has been shown to lengthen mean gestational age and lower the risk of preterm birth [75]. Research also suggests that folic acid, in combination with a multivitamin supplement, helps minimize the risk of congenital heart defects [1,2,14]. In a population-based case-control study in Atlanta, congenital heart defects were 24% less common in the infants of women who took multivitamins containing folic acid during the periconceptional period than in the infants of women who did not take multivitamins [76]. A case-control study conducted in California had similar results [77]. However, it is not possible to determine whether the findings from these studies could be attributed to components of multivitamins other than folic acid.

Studies have also found associations between the use of folic acid in combination with multivitamin supplements and reduced occurrence at birth of urinary tract anomalies, oral facial clefts, limb defects and hydrocephalus [2,14]. However, the results of these studies have been inconsistent [2].

Additional research is needed to fully understand the extent to which maternal consumption of folic acid might affect the risk of these adverse birth outcomes. However, folic acid's established role in preventing NTDs—and possibly other birth defects—underscores its importance during the periconceptional period.

Health Risks from Excessive Folate

Large amounts of folic acid can correct the megaloblastic anemia, but not the neurological damage, that can result from vitamin B12 deficiency. Some experts have therefore been concerned that high folic acid intakes might "mask" vitamin B12 deficiency until its neurological consequences become irreversible. But anemia is no longer the basis for diagnosing vitamin B12 deficiency, so the focus of concern has shifted to the possibility that large amounts of folic acid could precipitate or exacerbate the anemia and cognitive symptoms associated with vitamin B12 deficiency, perhaps by increasing homocysteine or methylmalonic acid concentrations [2,41,78-81]. However, the high homocysteine and methylmalonic acid concentrations in people with both low vitamin B12 and high folate concentrations could be due to severe malabsorptive conditions or pernicious anemia rather than high folic acid intakes [82,83]. High blood folate concentrations do not appear to exacerbate vitamin B12 deficiency in healthy, young adults [84].

Concerns have also been raised that high folic acid supplementation might accelerate the progression of preneoplastic lesions, increasing the risk of colorectal and possibly other forms of cancer in certain individuals [37-39].

Based on the metabolic interactions between folate and vitamin B12, the FNB established a UL for the synthetic forms of folate (i.e., folic acid) available in dietary supplements and fortified foods (Table 3) [2]. The FNB did not establish a UL for folate from food because high intakes of folate from food sources have not been reported to cause adverse effects [2]. The ULs do not apply to individuals taking high doses of folic acid under medical supervision [2].

Table 3: Tolerable Upper Intake Levels (ULs) for Folic Acid [2]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	Not possible to establish*	Not possible to establish*		
7–12 months	Not possible to establish*	Not possible to establish*		
1–3 years	300 mcg	300 mcg		
4– 8 years	400 mcg	400 mcg		
9–13 years	600 mcg	600 mcg		
14–18 years	800 mcg	800 mcg	800 mcg	800 mcg
19+ years	1,000 mcg	1,000 mcg	1,000 mcg	1,000 mcg

* Breast milk, formula, and food should be the only sources of folate for infants.

Interactions with Medications

Folic acid supplements can interact with several medications. A few examples are provided below. Individuals taking these medications on a regular basis should discuss their folate intakes with their healthcare providers.

Methotrexate

Methotrexate (Rheumatrex®, Trexall®), a medication used to treat cancer and autoimmune diseases, is a folate antagonist. Patients taking methotrexate for cancer should consult their oncologist before taking folic acid supplements because folic acid could interfere with methotrexate's anticancer effects [85]. However, for patients taking low-dose methotrexate for rheumatoid arthritis or psoriasis, folic acid supplements might reduce the gastrointestinal side effects of this medication [86,87].

Antiepileptic medications

Antiepileptic medications, such as phenytoin (Dilantin®), carbamazepine (Carbatrol®, Tegretol®, Equetro®, Epitol®), and valproate (Depacon®), are used to treat epilepsy, psychiatric diseases, and other medical conditions. These medications can reduce serum folate levels [88]. Furthermore, folic acid supplements might reduce serum levels of these medications, so patients taking antiepileptic drugs should check with their healthcare provider before taking folic acid supplements [85].

Sulfasalazine

Sulfasalazine (Azulfidine®) is used primarily to treat ulcerative colitis. It inhibits the intestinal absorption of folate and can cause folate deficiency [89]. Patients taking sulfasalazine should check with their healthcare provider about increasing their dietary folate intake, taking a folic acid supplement, or both [85].

Folate and Healthful Diets

The federal government's 2015-2020 *Dietary Guidelines for Americans* notes that "Nutritional needs should be met primarily from foods. … Foods in nutrient-dense forms contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects. In some cases, fortified foods and dietary supplements may be useful in providing one or more nutrients that otherwise may be consumed in less-than-recommended amounts."

For more information about building a healthy diet, refer to the *Dietary Guidelines for Americans* and the U.S. Department of Agriculture's MyPlate.

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

- Includes a variety of vegetables, fruits, whole grains, fat-free or low-fat milk and milk products, and oils.

  Many fruits and vegetables are good sources of folate. In the United States, bread, cereal, flour, cornmeal, pasta, rice, and other grain products are fortified with folic acid.

- Includes a variety of protein foods, including seafood, lean meats and poultry, eggs, legumes (beans and peas), nuts, seeds, and soy products.

  Beef liver contains high amounts of folate. Peas, beans, nuts, and eggs also have folate.

- Limits saturated and *trans* fats, added sugars, and sodium.

- Stays within your daily calorie needs.

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