National Institutes of Health
Office of Dietary Supplements

Folate

Fact Sheet for Health Professionals

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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" and sometimes "vitamin B9," is the generic term for naturally occurring food folates, and folates in dietary supplements and fortified foods, including folic acid. Food folates are in the tetrahydrofolate (THF) form and usually have additional glutamate residues, making them polyglutamates [1]. Folic acid is the fully oxidized monoglutamate form of the vitamin that is used in fortified foods and most dietary supplements. Some dietary supplements also contain folate in the monoglutamyl form, 5-MTHF (also known as L-5-MTHF, 5-methyl-folate, L-methylfolate, and methylfolate).

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. 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 [4].

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. Before entering the bloodstream, the enzyme dihydrofolate reductase reduces the monoglutamate form to THF and converts it to either methyl or formyl forms [1]. The main form of folate in plasma is 5-MTHF.

The activity of dihydrofolate reductase varies greatly among individuals [3]. When the capacity of dihydrofolate reductase is exceeded, unmetabolized folic acid can be present in the blood [1,5,6]. Whether unmetabolized folic acid has any biological activity or can be used as a biomarker of folate status is not known [7]. Folate is also synthesized by colonic microbiota and can be absorbed across the colon, although the extent to which colonic folate contributes to folate status is unclear [8]. The total body content of folate is estimated to be 15 to 30 mg; about half of this amount is stored in the liver and the remainder in blood and body tissues [1].

Serum folate concentrations are commonly used to assess folate status; a value above 3 ng/mL indicates adequacy [1,2,9]. This indicator, however, is sensitive to recent dietary intake, so it might not

reflect long-term status. Erythrocyte folate concentrations provide a longer-term measure of folate intakes; a concentration above 140 ng/mL indicates adequate folate status [2,3,7,9].

A combination of serum or erythrocyte folate 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-MTHF deficiency [9]. 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 [1,3,9,10]. The most commonly used cutoff value for elevated homocysteine levels is 16 micromol/L, although slightly lower values of 12 to 14 micromol/L have also been used [2]. A homocysteine cutoff of 10 micromol/L has been proposed for assessing folate status in populations [3].

Recommended Intakes

Intake recommendations for folate and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by an expert committee of the Food and Nutrition Board (FNB) at the National Academies of Sciences, Engineering, and Medicine [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 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 folate as 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 [1,2,4]. 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

Factors for converting mcg DFE to mcg for supplemental folate in the form of 5-MTHF have not been formally established [11].

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 (see Table 1).

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

Age	Male	Female	Pregnancy	Lactation
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 naturally present in a wide variety of foods, including vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, seafood, eggs, dairy products, meat, poultry, and grains (Table 2) [4,12]. Spinach, liver, asparagus, and brussels sprouts are among the foods with the highest folate levels.

In January 1998, the U.S. Food and Drug Administration (FDA) began requiring manufacturers to add 140 mcg folic acid/100 g to enriched breads, cereals, flours, cornmeals, pastas, rice, and other grain products [13] to reduce the risk of neural tube defects (NTDs). Because cereals and grains are widely consumed in the United States, these products have become important contributors of folic acid to the American diet. The fortification program increased mean folic acid intakes in the United States by about 190 mcg/day [14]. In April 2016, FDA approved the voluntary addition of up to 154 mcg folic acid/100 g to corn masa flour [15].

Since November 1, 1998, the Canadian government has also required the addition of 150 mcg folic acid/100 g to many grains, including enriched pasta, cornmeal, and white flour [6,16]. Many other countries, including Costa Rica, Chile, and South Africa, have also established mandatory folic acid fortification programs [6,17].

Table 2: Folate and Folic Acid Content of Selected Foods [12]

Food	Micrograms (mcg) DFE per serving	Percent DV*
Beef liver, braised, 3 ounces	215	54

Food	Micrograms (mcg) DFE per serving	Percent DV*
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	22
Asparagus, boiled, 4 spears	89	22
Brussels sprouts, frozen, boiled, ½ cup	78	20
Spaghetti, cooked, enriched, ½ cup†	74	19
Lettuce, romaine, shredded, 1 cup	64	16
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
Bread, white, 1 slice†	50	13
Green peas, frozen, boiled, ½ cup	47	12
Kidney beans, canned, ½ cup	46	12
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
Peanuts, dry roasted, 1 ounce	27	7
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
Cantaloupe, raw, cubed, ½ cup	17	4
Vegetarian baked beans, canned, ½ cup	15	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, 3 ounces	3	1

* DV = Daily Value. The 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 folate is 400 mcg DFE for adults

and children aged 4 years and older [11], where mcg DFE = mcg naturally occurring folate + (1.7 x mcg folic acid). The labels must list folate content in mcg DFE per serving and if folic acid is added to the product, they must also list the amount of folic acid in mcg in parentheses. The FDA does not require food labels to list folate content unless folic acid 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.

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

The U.S. Department of Agriculture's FoodData Central (https://fdc.nal.usda.gov/) [12] lists the nutrient content of many foods and provides a comprehensive list of foods containing folate arranged by nutrient content (https://ods.od.nih.gov/pubs/usdandb/Folate-Content.pdf) and by food name. (https://ods.od.nih.gov/pubs/usdandb/Folate-Food.pdf)

Dietary supplements

Folic acid is available in multivitamins and prenatal vitamins, supplements containing other B-complex vitamins, and supplements containing only folic acid. Common doses range from 680 to 1,360 mcg DFE (400 to 800 mcg folic acid) in supplements for adults and 340 to 680 mcg DFE (200 to 400 mcg folic acid) in children's multivitamins [18,19].

About 85% of supplemental folic acid, when taken with food, is bioavailable [2,4]. When consumed without food, nearly 100% of supplemental folic acid is bioavailable.

Dietary supplements containing 5-MTHF are also available. For some people, supplementation with 5-MTHF might be more beneficial than with folic acid (see "People with an *MTHFR* polymorphism" below) [20,21]. The bioavailability of 5-MTHF in supplements is the same as or greater than that of folic acid [22-27]. However, conversion factors between mcg and mcg DFE for 5-MTHF have not been formally established. The FDA allows manufacturers to use either a conversion factor of 1.7 to be comparable to folic acid, or their own established conversion factors not to exceed 1.7 [11].

Folate Intakes and Status

According to data from the 2013–2014 National Health and Nutrition Examination Survey (NHANES), most people in the United States consume adequate amounts of folate. Mean dietary intakes of folate from foods range from 417 to 547 mcg DFE per day for children aged 2–19 [28]. Average daily intakes of folate from food are 602 mcg DFE for males aged 20 and older and 455 mcg DFE for females.

Although most people consume adequate amounts of folate, certain groups, including women of childbearing age and non-Hispanic black women, are at risk of insufficient folate intakes. Even when intakes of folic acid from dietary supplements are included, 19% of female adolescents aged 14 to 18 years and 17% of women aged 19 to 30 years do not meet the EAR [29]. Similarly, 23% of non-Hispanic black women have inadequate total intakes, compared with 13% of non-Hispanic white women.

About 35% of adults and 28% of children aged 1 to 13 years in the United States use supplements containing folic acid [29,30]. 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. People aged 2 years and older who take supplements containing folic acid get a mean of 712 mcg DFE from those supplements [28].

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 [18]. 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 [31].

Some population groups are at risk of obtaining excessive folic acid. About 5% of men and women aged 51-70 and men aged 71 and older have folic acid intakes exceeding the UL of 1,000 mcg per day, primarily because of the folic acid they obtain from dietary supplements [29]. Furthermore, 30% to 66% of children aged 1 to 13 years who take folic acid-containing supplements have intakes of folic acid from both fortified food and dietary supplements exceeding the UL of 300–600 mcg per day [30]. Almost all children aged 1 to 8 years who consume at least 200 mcg/day folic acid from dietary supplements have total intakes that exceed the UL [18]. Little is known about the long-term effects of high folic acid doses in children [7].

Folate Deficiency

Isolated folate deficiency is uncommon; folate deficiency usually coexists with other nutrient deficiencies because of its strong association with poor diet, alcoholism, and malabsorptive disorders [4]. Megaloblastic anemia, which is characterized by large, abnormally nucleated erythrocytes, is the primary clinical sign of folate or vitamin B12 deficiency [1,4]. Its symptoms include weakness, fatigue, difficulty concentrating, irritability, headache, heart palpitations, and shortness of breath [2].

Folate deficiency can also produce soreness in and shallow ulcerations on the tongue and oral mucosa; changes in skin, hair, or fingernail pigmentation; gastrointestinal symptoms; and elevated blood concentrations of homocysteine [1,2,4,32].

Women with insufficient folate intakes are at increased risk of giving birth to infants with NTDs [2]. Inadequate maternal folate status has also been associated with low infant birth weight, preterm delivery, and fetal growth retardation [1,33].

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 use disorder

People with alcohol use disorder frequently have poor-quality diets that contain insufficient amounts of folate. Moreover, alcohol interferes with folate absorption and hepatic uptake, accelerates folate breakdown, and increases its renal excretion [1,4,9]. An evaluation in Portugal, where the food supply is

not fortified with folic acid, found low folate status in more than 60% of people with chronic alcoholism [34]. 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 to levels below the cutoff for folate adequacy of 3 ng/ml [35].

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 [2,36,37]. However, some women of childbearing age get insufficient amounts of folate even if they take dietary supplements [29]. Women of childbearing age should obtain 400 mcg/day folic acid from dietary supplements and/or fortified foods in addition to the folate provided by a varied diet [2].

Pregnant women

During pregnancy, demands for folate increase because of its role in nucleic acid synthesis [33]. To meet this need, the FNB increased the folate RDA from 400 mcg DFE/day for nonpregnant women to 600 mcg DFE/day during pregnancy [2]. This level of intake might be difficult for some 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 [38].

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 absorb less folate than people without these disorders [4]; for example, about 20–60% of patients with inflammatory bowel disease have folate deficiency [39]. Diminished gastric acid secretion associated with atrophic gastritis, gastric surgery, and other conditions can also reduce folate absorption [4].

People with an MTHFR polymorphism

People with a genetic polymorphism, 677C>T, in the *methylenetetrahydrofolate reductase (MTHFR)* gene have a reduced ability to convert folate to one of its active forms, 5-MTHF, because the methylenetetrahydrofolate reductase enzyme needed for this conversion is less active [21]. About 25% of Hispanics, 10% of Caucasians and Asians, and 1% of African Americans are homozygous for the 677C>T *MTHFR* polymorphism [27]. This polymorphism results in less biologically available 5-MTHF and, thus, reduced methylation potential, leading to elevated homocysteine levels and an increased risk of NTDs [1,3,20,40]. Although the research on the benefits of folate supplementation for people with this genetic polymorphism is inconclusive, some of these people might benefit from supplementation with 5-MTHF [20,21]. However, the Centers for Disease Control and Prevention (CDC) recommends 400 mcg/day of folic acid, not 5-MTHF, for people who could become pregnant, even if they have a 677C>T *MTHFR* polymorphism (see "NTDs" below) [41].

Folate and Health

This section focuses on seven diseases and disorders in which folate might play a role: autism spectrum disorder; cancer; cardiovascular disease and stroke; dementia, cognitive function, and

Alzheimer's disease; depression; NTDs; and preterm birth, congenital heart defects, and other congenital anomalies.

Autism spectrum disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulty communicating and interacting with other people, limited interests, and repetitive behaviors. The classification and diagnosis of ASD was changed in 2013 to include conditions previously known as autistic disorder, Asperger's syndrome, and pervasive developmental disorder not otherwise specified [42]. The causes of ASD are not clear, but genetic and environmental factors (including infections) and prenatal exposure to certain drugs, pollutants, and pesticides are believed to play a role [43-46].

Emerging evidence suggests that periconceptional folic acid supplementation might reduce the risk of ASD or mitigate the potentially increased risk of ASD from prenatal exposure to certain drugs and toxic chemicals. The mechanism of these potential benefits is unknown, but it might be related to folic acid's role in DNA methylation, which, in turn, can affect neurodevelopment [47-49].

Some, but not all, observational studies have shown associations between maternal use of folic acid and/or multivitamin supplements before and/or during pregnancy and lower risk of ASD in the women's offspring. For example, the prospective Norwegian Mother and Child Cohort Study that included 85,176 children aged 3.3 to 10.2 years found that children of mothers who took up to 400 mcg per day folic acid during all of part of the time from 4 weeks before to 8 weeks after the start of pregnancy were 39% less likely to have autistic disorder than those whose mothers did not take the supplements [50]. The results showed no significant associations, however, between supplementation and Asperger's syndrome or pervasive developmental disorder not otherwise specified. In a U.S. population-based, case-control study of 837 children, those born to mothers who consumed a mean of 600 mcg folic acid per day or more from supplements and fortified breakfast cereals during the first month of pregnancy had a 38% lower risk of ASD than those of mothers who consumed less than 600 mcg per day [51]. This association was strongest for mothers and children with the 677C>T *MTHFR* polymorphism. Similarly, a 2018 case-control cohort study of 45,300 Israeli children demonstrated a significantly decreased risk of ASD in children of mothers who took folic acid and/or multivitamin supplements before and/or during pregnancy [52]. Conversely, a longitudinal, population-based cohort of 35,059 pregnant Danish women and their children found no association between periconceptional folic acid or multivitamin use and ASD [53].

Periconceptional use of folic acid might mitigate the potentially increased risk of ASD in children exposed to certain drugs and neurotoxins in utero [44-46]. An analysis of data from the Norwegian Mother and Child Cohort Study, which included 104,946 children, found that children exposed to antiepileptic drugs (known to reduce folate in vivo) in utero were 5.9 to 7.9 times more likely to have autistic traits at ages 18 and 36 months if their mothers did not take folic acid periconceptionally than if they did [44]. In addition, the severity of autistic traits was inversely associated with both maternal plasma folate concentrations and folic acid doses. Similarly, in a U.S. study of 712 children, mothers exposed to any indoor pesticide during pregnancy who had folic acid intakes of 800 mcg or more per day during the first month of pregnancy were 1.7 times more likely to have a child with ASD than

women with the same folic acid intakes who were not exposed to indoor pesticides [45]. The risk of ASD was even higher (2.5 times) if the women were exposed to indoor pesticides and had daily folic acid intakes of less than 800 mcg, suggesting that folic acid might attenuate the potentially increased risk of ASD from pesticide exposure.

Overall, the evidence to date suggests a possible inverse association between mothers' periconceptional folic acid intakes and risk of ASD in their offspring. However, most, if not all, of the currently available data are observational, and confounding weakens the ability to demonstrate causal inference. Additional research and validation in other studies are needed before firm conclusions can be drawn.

Cancer

Several epidemiological studies have suggested an inverse association between folate intakes and status and the risk of colorectal, lung, pancreatic, esophageal, stomach, cervical, ovarian, breast, bladder, and other cancers [1,9,54,55]. Research has not established the precise nature of folate's effect on carcinogenesis, but scientists hypothesize that folate might influence cancer development through its role in one-carbon metabolism and subsequent effects on DNA replication and cell division [55,56]. Evidence also indicates that folate might play a dual role in cancer initiation and progression [57]. That is, folate might suppress some types of cancer during the early stages of development, whereas high doses of folic acid taken after preneoplastic lesions have been established might promote cancer development and progression.

Results from clinical trials involving folic acid supplementation have been mixed. In addition, most trials have included other B-vitamins (frequently at doses well above RDA levels) and sometimes other nutrients, making it difficult to disentangle the effects, if any, of folic acid alone. For example, in a trial in France, 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 [58]. The researchers found no association between B-vitamin supplementation and cancer outcomes. In a combined analysis of two trials in Norway (where foods are not fortified with folic acid), supplementation with 800 mcg/day folic acid plus 400 mcg/day vitamin B12 for a median of 39 months in 3,411 people with ischemic heart disease increased cancer incidence rates by 21% and cancer mortality rates by 38% compared with no supplementation [59]. Findings from these Norwegian trials have raised concerns about folic acid supplementation's potential to raise cancer risk.

The most thorough research has focused on folate's effect on the development of colorectal cancer and its precursor, adenoma [1,55,60]. Several epidemiological studies have found inverse associations between high dietary folate intakes and the risk of colorectal adenoma and cancer [61-64]. 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 lower than 200 mcg/day [62]. Other studies, however, have found no significant associations between dietary folate intakes [65,66] or circulating folate concentrations [67,68] and colorectal cancer risk.

Several clinical trials have examined whether supplemental folic acid (sometimes in combination with other B-vitamins) 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 rates of colorectal adenoma during 7.3 years of intervention and about 2 years of postintervention follow-up [69]. A pooled analysis of three large clinical trials (one 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 adenoma recurrence rates in people with a history of adenoma [70]. However, in one of the studies included in the analysis, folic acid supplementation (1,000 mcg/day) significantly increased the risks of having three or more adenomas and of noncolorectal cancers, although it had no effect on colorectal cancer risk [71].

Folic acid supplementation also had no effect on the risk of all cancer types combined in the pooled analysis of three clinical trials cited above [70]. Similarly, a meta-analysis of 13 randomized trials showed no statistically significant effects of folic acid supplementation (median daily dose of 2,000 mcg) over an average treatment period of 5.2 years on overall cancer incidence or the incidence of colorectal, lung, breast, prostate, or other cancers [72].

Some research has found associations between folic acid supplementation and increased cancer risk. In a randomized clinical trial investigating osteoporotic fracture incidence in 2,919 participants aged 65 years or older with elevated homocysteine levels, those who received 400 mcg folic acid plus 500 mcg vitamin B12 and 600 IU vitamin D3 for 2 years reported a significantly higher cancer incidence, especially of colorectal and other gastrointestinal cancers, than those who received only 600 IU vitamin D3 [73]. In addition, a 2018 prospective study found that folic acid intake from fortified foods and supplements was positively associated with a risk of cancer recurrence among 619 patients with non–muscle-invasive bladder cancer, whereas natural folate intakes showed no significant association [74]. Higher plasma folate concentrations have also been associated with an increased risk of breast cancer in women with a *BRCA1* or *BRCA2* mutation [75]. A secondary analysis of the study by Cole and colleagues [71] found that folic acid supplementation significantly increased the risk of prostate cancer [76] . Subsequent research has shown an association between increased cancer cell proliferation and higher serum folate concentrations in men with prostate cancer [77]. A meta-analysis of six randomized controlled trials that included a total of 25,738 men found that the risk of prostate cancer was 24% higher in men receiving folic acid supplements than those taking a placebo [78].

The mixed findings from clinical trials, combined with evidence from laboratory and animal studies indicating that high folate status promotes tumor progression, suggest that folate might play dual roles in cancer risk, depending on the dosage and timing of the exposure. Modest doses of folic acid taken before preneoplastic lesions are established might suppress cancer development in healthy tissues, whereas high doses taken after the establishment of preneoplastic lesions might promote cancer development and progression [9,60,79-82]. 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 pre-adenoma stages [83].

A 2015 expert panel convened by the National Toxicology Program and the National Institutes of Health Office of Dietary Supplements concluded that folic acid supplements do not reduce cancer risk in people with adequate baseline folate status. The panel also determined that the consistent findings from human studies that supplemental folic acid has an adverse effect on cancer growth justify additional research on the effects of folic acid supplementation on cancer risk [84]. Several important questions about these effects remain, including the dose and timing of folic acid supplementation that might exert tumor-promoting effects and whether this effect is specific to synthetic folic acid or other forms of folate [57].

Overall, the evidence to date indicates that adequate dietary folate intake might reduce the risk of some forms of cancer. However, the effects of supplemental folic acid on cancer risk are unclear, especially among individuals with a history of colorectal adenomas or other forms of cancer. More research is needed to fully understand how dietary folate and supplemental folic acid affect cancer risk and whether their effects differ by timing of exposure.

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 these micronutrients reduce cardiovascular disease risk by lowering homocysteine levels [1,85].

Folic acid (and vitamin B12) supplements lower homocysteine levels. However, these supplements do not actually decrease the risk of cardiovascular disease, although they appear to provide protection from stroke [85-94]. For example, in 5,442 U.S. women aged 42 or older who were at high risk of cardiovascular disease, daily supplements containing 2,500 mcg folic acid, 1 mg vitamin B12, and 50 mg vitamin B6 for 7.3 years did not reduce the risk of major cardiovascular events [89]. In a substudy of 300 participants, the supplementation also had no significant effects on biomarkers of vascular inflammation [91], but it did lower homocysteine levels by a mean of 18.5% [89]. Another clinical trial included 5,522 patients aged 55 years or older with vascular disease or diabetes from various countries (including the United States and Canada) that had a folic acid fortification program and some that did not [88]. 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 by 25%.

In a large trial in regions of China without folic acid fortification among 20,702 adults with hypertension but no history of stroke or myocardial infarction, supplementation with 800 mcg folic acid plus 10 mg enalapril (used to treat high blood pressure) for a median of 4.5 years significantly reduced the risk of stroke by 21% compared with enalapril alone [92]. The effect was more pronounced in participants with the lowest baseline levels of plasma folate. An analysis of 10,789 participants from this trial found that folic acid supplementation significantly reduced the risk of stroke by 73% among those who had a low platelet count and an elevated homocysteine level (increasing their risk of stroke) but had no significant effect on participants with a high platelet count and low homocysteine level [95]. These

findings suggest that folic acid supplementation might primarily benefit those with insufficient folate levels, which are less common in countries, such as the United States, with folic acid fortification [96].

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% [86]. Likewise, the authors of the third update of a Cochrane review of the effects of homocysteine-lowering interventions on cardiovascular events concluded that folic acid supplementation alone or in combination with vitamin B6 and vitamin B12 does not affect the risk of myocardial infarction or death from any cause, but it does reduce the risk of stroke [97]. Three other meta-analyses have also found that folic acid is effective for preventing stroke, especially in populations exposed to no or partial folic acid fortification [94,98,99].

Overall, the available evidence suggests that supplementation with folic acid alone or in combination with other B-vitamins reduces the risk of stroke, especially in populations with low folate status, but does not affect other cardiovascular endpoints.

Dementia, cognitive function, and Alzheimer's disease

Most observational studies conducted to date have shown positive associations between elevated homocysteine levels and the incidence of both Alzheimer's disease and dementia [32,79,100-104]. 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 [103]. 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 [79,100,101,103,105].

Despite this evidence, most clinical trial research has not shown that folic acid supplementation affects cognitive function or the development of dementia or Alzheimer's disease, even though supplementation lowers homocysteine levels. In one randomized, double-blind, placebo-controlled trial in the Netherlands, 195 people aged 70 years or older with no or moderate cognitive impairment received 400 mcg folic acid plus 1 mg vitamin B12; 1 mg vitamin B12; or placebo for 24 weeks [106. Treatment with folic acid plus vitamin B12 reduced homocysteine concentrations by 36% but did not improve cognitive function. In another clinical trial in older adults (mean age 74.1 years) with elevated homocysteine levels, supplementation with 400 mcg folic acid plus 500 mcg vitamin B12 and 600 IU vitamin D3 for 2 years lowered homocysteine levels but did not affect cognitive performance compared with 600 IU vitamin D3 alone [107].

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 [108]. 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 [109].

A secondary analysis of a study in Australia (which did not have mandatory folic acid fortification at the time of the study) 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 [110]. Another meta-analysis included 11 randomized controlled trials in over 20,000 older adults (mean age 60–82 years) that administered 400 to 2,500 mcg folic acid plus 20–1,000 mcg vitamin B12 in 10 trials and 3–50 mg vitamin B6 in 8 trials for 0.3 to 7.1 years. The supplementation significantly lowered homocysteine levels but did not affect cognitive aging, global cognitive function, or specific cognitive domains (including memory, speed, and executive function) [111].

Several large reviews have evaluated the effect of B vitamins on cognitive function. Most of the authors concluded that supplementation with folic acid alone or in combination with vitamins B12 or B6 does not appear to improve cognitive function in individuals with or without cognitive impairment [112-115]. Some noted, however, that when researchers took baseline homocysteine and B-vitamin status into account, B-vitamin supplementation slowed cognitive decline in individuals at high risk of cognitive decline [103,104]. For example, one trial in the Netherlands administered either 800 mcg folic acid or placebo daily for 3 years to 818 participants aged 50–70 years with elevated homocysteine levels (13 micromol/L or higher) and normal vitamin B12 levels [116]. Folic acid supplementation reduced homocysteine concentrations by 26% and significantly improved global cognitive function, memory, and information processing speed compared with placebo, but it did not affect sensorimotor speed, complex speed, or word fluency.

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

Depression

Low folate status has been linked to depression and poor response to antidepressants in some, but not all, studies. The possible mechanisms are unclear but might be related to folate's role in methylation reactions in the brain, neurotransmitter synthesis, and homocysteine metabolism [117,118]. However, secondary factors linked to depression, such as unhealthy eating patterns and alcohol use disorder, might also contribute to the observed association between low folate status and depression [119.

In an ethnically diverse population study of 2,948 people aged 15 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 [119]. An analysis of 2005-2006 NHANES data found that higher serum concentrations of folate were associated with a lower prevalence of depression in 2,791 adults aged 20 or older [117]. The association was statistically significant in females, but not in males. However, another analysis showed no associations between folate intakes from both food and dietary supplements and depression among 1,368 healthy Canadians aged 67–84 years [118]. Results from a study of 52 men and women with major depressive disorder showed that

only 1 of 14 participants with low serum folate levels responded to antidepressant treatment compared with 17 of 38 with normal folate levels [120].

A few studies have examined whether folate status affects the risk of depression during pregnancy or after childbirth. A systematic review of these studies had mixed results [121]. One study included in the review among 709 women in Singapore found that compared with women with higher plasma folate concentrations (mean 40.4 nmol/L [17.8 ng/mL]) at 26–28 weeks' gestation, those with lower plasma folate concentrations (mean 27.3 nmol/L [12.0 ng/mL]) had a significantly higher risk of depression during pregnancy but not after giving birth [122]. Another study of 2,856 women in the United Kingdom found no significant associations between red blood cell folate levels or folate intakes from food and dietary supplements before or during pregnancy and postpartum depressive symptoms [123]. More recently, a cohort study of 1,592 Chinese women found a lower prevalence of postpartum depression in women who took folic acid supplements for more than 6 months during pregnancy than in those who took them for less time [124].

Studies have had mixed results on whether folic acid supplementation might be a helpful adjuvant treatment for depression when used with traditional antidepressant medications. In a clinical trial 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 daily for 10 weeks [125]. 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. Another clinical trial in the United Kingdom randomized 475 adults with moderate to severe depression who were taking antidepressant medications to either 5,000 mcg folic acid or placebo daily for 12 weeks in addition to their antidepressants [126]. Measures of depression did not improve in participants taking folic acid compared with those taking placebo. The authors of a systematic review and meta-analysis of four trials of folic acid (<5,000 mcg/day in two trials; =5,000 mcg/day in two trials) in combination with fluoxetine or other antidepressants in patients with major depressive disorder concluded that less than 5,000 mcg/day folic acid might be beneficial as an adjunct to serotonin reuptake inhibitor (SSRI) therapy [127]. The authors noted, however, that this conclusion was based on low-quality evidence. Another meta-analysis of four clinical trials found that 500–10,000 mcg folic acid per day for 6–12 weeks as an adjunctive treatment did not significantly affect measures of depression compared with placebo [128].

Other studies have examined the effects of 5-MTHF supplementation as an adjuvant treatment to antidepressants, and results suggest that it might have more promise than folic acid [127-130]. In a clinical trial in 148 adults with major depressive disorder, supplementation with 7,500 mcg/day 5-MTHF for 30 days followed by 15,000 mcg/day for another 30 days, both in conjunction with SSRI treatment, did not improve measures of depression compared with SSRI treatment plus placebo [131]. However, in a subsequent trial with the same study design in 75 adults, supplementation with 15,000 mcg/day 5-MTHF plus SSRI treatment for the full 60 days did significantly improve depression compared with SSRI treatment plus placebo [131].

The authors of a systematic review and meta-analysis of three trials of 5-MTHF (<15,000 mcg/day in one trial, and 15,000 mcg/day in two trials) in combination with fluoxetine or other antidepressants, concluded that 15,000 mcg/day 5-MTHF might be an effective adjunct to SSRI therapy in patients with major depressive disorder, although they noted that this conclusion was based on low-quality evidence [127]. In addition, evidence-based guidelines from the British Association for Psychopharmacology [129] and the Canadian Network for Mood and Anxiety Treatments [130] state that 5-MTHF might be effective as an adjunct to SSRI treatment for depressive disorders.

Additional research is needed to fully understand the association between folate status and depression. Although limited evidence suggests that supplementation with certain forms and doses of folate might be a helpful adjuvant treatment for depressive disorders, more research is needed to confirm these findings. In addition, many of the doses of folate used in studies of depression exceed the UL and should be taken only under medical supervision.

NTDs

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 on days 21 to 28 after conception [132,133]. The prevalence rate of spina bifida and anencephaly (the two most common types of NTDs) in the United States is 5.5 to 6.5 per 10,000 births [134].

Because of its role in the synthesis of DNA and other critical cell components, folate is especially important during phases of rapid cell growth [135]. Although the mechanism has not been fully established, clinical trial evidence shows that adequate periconceptional folic acid consumption by women prevents a substantial proportion of NTDs [3,81,132,133,136,137].

Since 1998, when mandatory folic acid fortification began in the United States, NTD rates have declined by 28% [134]. However, significant racial and ethnic disparities persist. NTD prevalence rates are highest among Hispanic women and lowest among non-Hispanic black women. Factors that might contribute to these disparities include differences in dietary and supplement-taking practices [138] as well as factors other than folate status—such as maternal diabetes, obesity, and intake of other nutrients (e.g., vitamin B12)—which are also believed to affect the risk of NTDs [132,137,139-141]. In addition, women with the 677C>T *MTHFR* polymorphism—which is more common in Hispanics than Caucasians, Asians, and African Americans—might have an increased risk of NTDs [1,3,27,40]. Another consideration is the fact that the data on NTD prevalence rates were collected before 2016, when FDA approved the voluntary addition of folic acid to corn masa flour [15], an ingredient commonly consumed by Hispanic populations. Whether this policy change has affected the disparities in NTD rates between Hispanic women and other populations is not yet known.

Because approximately 50% of pregnancies in the United States are unplanned, adequate folate status is especially important during the periconceptional period before a woman might be aware that she is pregnant. The FNB advises women capable of becoming pregnant to “consume 400 mcg of folic acid 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 CDC have published similar recommendations [36]. Consuming 400 mcg/day folic acid helps prevent NTDs, even in people with the 677C>T *MTHFR* polymorphism [41].

The authors of a 2017 systematic review concluded that folic acid supplementation protected users from NTDs in studies conducted before food fortification with folic acid began in the United States [142]. Although studies conducted since that time do not demonstrate a clear protective association (possibly because of food fortification effects, study design flaws, or inadequate sample sizes) [142], the U.S. Preventive Services Task Force recommends that all women who are planning to become or capable of becoming pregnant take a daily supplement containing 400 to 800 mcg folic acid starting least 1 month before conception and continuing through the first 2 to 3 months of pregnancy [37].

The FNB has not issued recommendations for women who have given birth to a child with an NTD and plan to become pregnant again. However, other experts recommend that these women obtain 4,000 to 5,000 mcg supplemental folic acid daily starting at least 1 to 3 months before conception and continuing for 2½ to 3 months after conception [132,143]. These doses exceed the UL and should be taken only under medical supervision [143].

Preterm birth, congenital heart defects, and other congenital anomalies

According to observational studies, folic acid supplementation might increase mean gestational age and lower the risk of preterm birth [1,144]. In addition, folic acid in combination with a multivitamin supplement helps minimize the risk of congenital heart defects, possibly because cardiac tissue development depends on cells that require large amounts of folate [1,2,132].

The authors of a large population-based cohort study of about 98% of all births in Canada from 1990 to 2011 concluded that folic acid fortification of foods was associated with an 11% reduction in the rate of nonchromosomal congenital heart defects [145]. In a population-based case-control study in Atlanta involving 3,987 infants, 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 [146]. A case-control study in California in 866 infants had similar results [147]. 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, but the results of these studies have been inconsistent [2,132].

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 folate 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 intakes

of folate supplements might “mask” vitamin B12 deficiency until its neurological consequences become irreversible. Questions about this possibility still remain, but the focus of concern has shifted to the potential for large amounts of folate to precipitate or exacerbate the anemia and cognitive symptoms associated with vitamin B12 deficiency [2,85,148-153].

Concerns have also been raised that high folic acid intakes might accelerate the progression of preneoplastic lesions, increasing the risk of colorectal and possibly other cancers in certain individuals [1,3,60,80,81]. In addition, intakes of 1,000 mcg per day or more of folic acid from supplements during the periconception period have been associated with lower scores on several tests of cognitive development in children at ages 4–5 years than in children of mothers who took 400 mcg to 999 mcg [154].

Intakes of folic acid that exceed the body’s ability to reduce it to THF lead to unmetabolized folic acid in the body, which has been linked to reduced numbers and activity of natural killer cells, suggesting that it could affect the immune system [5,155]. In addition, some scientists have hypothesized that unmetabolized folic acid might be related to cognitive impairment among older adults [156]. These potential negative health consequences are not well understood and warrant further research [1,9].

Studies have found unmetabolized folic acid in blood from children, adolescents, and adults [1,5,157,158]; breastmilk [159]; and cord blood from newborns [160,161]. Limited research suggests that single doses of 300 mcg or 400 mcg folic acid (a common amount in folic acid-containing supplements or servings of fortified foods, such as breakfast cereals) result in detectable serum levels of unmetabolized folic acid, whereas doses of 100 mcg or 200 mcg do not [162,163]. In addition, a dose-frequency interaction appears to occur in which smaller amounts of folic acid consumed more frequently produce higher unmetabolized folic acid concentrations than the same total dose consumed in larger, less frequent amounts [164].

Based on the metabolic interactions between folate and vitamin B12, the FNB established a UL for the synthetic forms of folate 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]. Thus, unlike the RDAs, the ULs are in mcg, not mcg DFE. For folic acid, 1,000 mcg is equivalent to 1,667 mcg DFE because 0.6 mcg folic acid = 1 mcg DFE [11,164]. The ULs do not apply to individuals taking high doses of supplemental folate under medical supervision [2].

Table 3: Tolerable Upper Intake Levels (ULs) for Folate from Supplements or Fortified Foods [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

Folate 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 health care providers.

Methotrexate

Methotrexate (Rheumatrex®, Trexall®), used to treat cancer and autoimmune diseases, is a folate antagonist. Patients taking methotrexate for cancer should consult their oncologist before taking folate supplements because the supplements could interfere with methotrexate's anticancer effects [166]. However, folate supplements might reduce the gastrointestinal side effects of low-dose methotrexate taken for rheumatoid arthritis or psoriasis [167,168].

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 [169]. Furthermore, folate supplements might reduce serum levels of these medications, so patients taking antiepileptic drugs should check with their health care provider before taking folate supplements [166].

Sulfasalazine

Sulfasalazine (Azulfidine®) is used primarily to treat ulcerative colitis. It inhibits the intestinal absorption of folate and can cause folate deficiency [170]. Patients taking sulfasalazine should ask their health care provider whether they should increase their dietary folate intake, start taking a folate supplement, or both [166].

Folate 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.

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 such as lean meats; poultry; eggs; seafood; beans, peas, and lentils; nuts and seeds; and soy products.

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

- Limits foods and beverages higher in added sugars, saturated fat, and sodium.

- Limits alcoholic beverages.

- Stays within your daily calorie needs.

References

1. Bailey LB, Caudill MA. Folate. In: Erdman JW, Macdonald IA, Zeisel SH, eds. Present Knowledge in Nutrition. 10th ed. Washington, DC: Wiley-Blackwell; 2012:321-42.
2. 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.
3. Stover PJ. Folic acid. In: Ross AC, Caballero B, Cousins RJ, Tucker KL, Ziegler TR, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2012:358-68.
4. Carmel R. Folic acid. In: Shils M, Shike M, Ross A, Caballero B, Cousins RJ, eds. Modern Nutrition in Health and Disease. 11th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2005:470-81.
5. Paniz C, Bertinato JF, Lucena MR, et al. A daily dose of 5 mg folic acid for 90 days is associated with increased serum unmetabolized folic acid and reduced natural killer cell cytotoxicity in healthy Brazilian adults. J Nutr 2017;147:1677-85. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28724658?dopt=Abstract)]
6. Crider KS, Bailey LB, Berry RJ. Folic acid food fortification-its history, effect, concerns, and future directions. Nutrients 2011;3:370-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22254102?dopt=Abstract)]
7. Yetley EA, Pfeiffer CM, Phinney KW, et al. Biomarkers of folate status in NHANES: a roundtable summary. Am J Clin Nutr 2011;94:303S-12S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21593502?dopt=Abstract)]
8. Lakoff A, Fazili Z, Aufreiter S, et al. Folate is absorbed across the human colon: evidence by using enteric-coated caplets containing 13C-labeled [6S]-5-formyltetrahydrofolate. Am J Clin Nutr

2014;100:1278-86. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25332326?dopt=Abstract)]

9. Bailey LB, Stover PJ, McNulty H, et al. Biomarkers of nutrition for development-folate review. J Nutr 2015;145:1636S-80S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/26451605?dopt=Abstract)]

10. Green R. Indicators for assessing folate and vitamin B-12 status and for monitoring the efficacy of intervention strategies. Am J Clin Nutr 2011;94:666S-72S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21733877?dopt=Abstract)]

11. U.S. Food and Drug Administration. Food Labeling: Revision of the Nutrition and Supplement Facts Labels. (https://www.federalregister.gov/documents/2016/05/27/2016-11867/food-labeling-revision-of-the-nutrition-and-supplement-facts-labels)2016.

12. U.S. Department of Agriculture, Agricultural Research Service. FoodData Central (https://fdc.nal.usda.gov/), 2019.

13. U.S. Food and Drug Administration. Food Standards: Amendment of Standards of Identity For Enriched Grain Products to Require Addition of Folic Acid. (https://www.govinfo.gov/content/pkg/FR-1996-03-05/pdf/96-5014.pdf) Federal Register 1996;61:8781-97.

14. Choumenkovitch SF, Selhub J, Wilson PW, et al. Folic acid intake from fortification in United States exceeds predictions. J Nutr 2002;132:2792-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/12221247?dopt=Abstract)]

15. U.S. Food and Drug Administration. FDA approves folic acid fortification of corn masa flour. (https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm496104.htm) 2016. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20703205?dopt=Abstract)]

16. Government of Canada. Regulations amending the food and drug regulations (1066). Canada Gazette 1998;132.

17. Centers for Disease Control and Prevention. CDC grand rounds: Additional opportunities to prevent neural tube defects with folic acid fortification. MMWR Morb Mortal Wkly Rep 2010;59:980-4. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20703205?dopt=Abstract)]

18. Yeung LF, Cogswell ME, Carriquiry AL, et al. Contributions of enriched cereal-grain products, ready-to-eat cereals, and supplements to folic acid and vitamin B-12 usual intake and folate and vitamin B-12 status in US children: National Health and Nutrition Examination Survey (NHANES), 2003-2006. Am J Clin Nutr 2011;93:172-85. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21084645?dopt=Abstract)]

19. National Institutes of Health. Dietary Supplement Label Database. (https://dsld.od.nih.gov) 2018.

20. Scaglione F, Panzavolta G. Folate, folic acid and 5-methyltetrahydrofolate are not the same thing. Xenobiotica 2014;44:480-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/24494987?

dopt=Abstract)]

21. Greenberg JA, Bell SJ, Guan Y, et al. Folic acid supplementation and pregnancy: more than just neural tube defect prevention. Rev Obstet Gynecol 2011;4:52-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22102928?dopt=Abstract)]

22. Henderson AM, Aleliunas RE, Loh SP, et al. l-5-Methyltetrahydrofolate supplementation increases blood folate concentrations to a greater extent than folic acid supplementation in Malaysian women. J Nutr 2018;148:885-90. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29878267?dopt=Abstract)]

23. Green TJ, Liu Y, Dadgar S, et al. Wheat rolls fortified with microencapsulated L-5-methyltetrahydrofolic acid or equimolar folic acid increase blood folate concentrations to a similar extent in healthy men and women. J Nutr 2013;143:867-71. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23616513?dopt=Abstract)]

24. Venn BJ, Green TJ, Moser R, et al. Comparison of the effect of low-dose supplementation with L-5-methyltetrahydrofolate or folic acid on plasma homocysteine: a randomized placebo-controlled study. Am J Clin Nutr 2003;77:658-62. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/12600857?dopt=Abstract)]

25. Venn BJ, Green TJ, Moser R, et al. Increases in blood folate indices are similar in women of childbearing age supplemented with [6S]-5-methyltetrahydrofolate and folic acid. J Nutr 2002;132:3353-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/12421850?dopt=Abstract)]

26. Lamers Y, Prinz-Langenohl R, Bramswig S, et al. Red blood cell folate concentrations increase more after supplementation with [6S]-5-methyltetrahydrofolate than with folic acid in women of childbearing age. Am J Clin Nutr 2006;84:156-61. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16825690?dopt=Abstract)]

27. Pietrzik K, Bailey L, Shane B. Folic acid and L-5-methyltetrahydrofolate: comparison of clinical pharmacokinetics and pharmacodynamics. Clin Pharmacokinet 2010;49:535-48. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20608755?dopt=Abstract)]

28. U.S. Department of Agriculture, Agricultural Research Service. What We Eat in America, 2013-2014. (http://www.ars.usda.gov/Services/docs.htm?docid=18349) 2017.

29. Bailey RL, Dodd KW, Gahche JJ, et al. Total folate and folic acid intake from foods and dietary supplements in the United States: 2003-2006. Am J Clin Nutr 2010;91:231-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19923379?dopt=Abstract)]

30. Bailey RL, McDowell MA, Dodd KW, et al. Total folate and folic acid intakes from foods and dietary supplements of US children aged 1-13 y. Am J Clin Nutr 2010;92:353-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20534747?dopt=Abstract)]

31. Yang Q, Cogswell ME, Hamner HC, et al. Folic acid source, usual intake, and folate and vitamin B-12 status in US adults: National Health and Nutrition Examination Survey (NHANES) 2003-2006.

Am J Clin Nutr 2010;91:64-72. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19828716?dopt=Abstract)]

32. Ho RC, Cheung MW, Fu E, et al. Is high homocysteine level a risk factor for cognitive decline in elderly? A systematic review, meta-analysis, and meta-regression. Am J Geriatr Psychiatry 2011;19:607-17. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21705865?dopt=Abstract)]

33. Scholl TO, Johnson WG. Folic acid: influence on the outcome of pregnancy. Am J Clin Nutr 2000;71:1295S-303S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/10799405?dopt=Abstract)]

34. Gloria L, Cravo M, Camilo ME, et al. Nutritional deficiencies in chronic alcoholics: relation to dietary intake and alcohol consumption. Am J Gastroenterol 1997;92:485-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/9068475?dopt=Abstract)]

35. Gibson A, Woodside JV, Young IS, et al. Alcohol increases homocysteine and reduces B vitamin concentration in healthy male volunteers--a randomized, crossover intervention study. QJM 2008;101:881-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18790817?dopt=Abstract)]

36. Centers for Disease Control and Prevention. Folic acid 2012. (https://www.cdc.gov/ncbddd/folicacid/recommendations.html)

37. U. S. Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Folic acid supplementation for the prevention of neural tube defects: US Preventive Services Task Force recommendation statement. JAMA 2017;317:183-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28097362?dopt=Abstract)]

38. American College of Obstetricians and Gynecologists. Frequently Asked Questions, FAQ001, Pregnancy, Nutrition During Pregnancy. (https://www.acog.org/~/media/For%20Patients/faq001.pdf?dmc=1&ts=20120515T1154495022) 2018.

39. Rossi RE, Whyand T, Murray CD, et al. The role of dietary supplements in inflammatory bowel disease: a systematic review. Eur J Gastroenterol Hepatol 2016;28:1357-64. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27769076?dopt=Abstract)]

40. Molloy AM, Pangilinan F, Brody LC. Genetic risk factors for folate-responsive neural tube defects. Annu Rev Nutr 2017;37:269-91. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28628360?dopt=Abstract)]

41. Centers for Disease Control and Prevention. MTHFR Gene, Folic Acid, and Preventing Neural Tube Defects. (https://www.cdc.gov/ncbddd/folicacid/mthfr-gene-and-folic-acid.html) 2022.

42. National Institute of Mental Health. Autism spectrum disorder. (https://www.nimh.nih.gov/health/topics/autism-spectrum-disorders-asd/index.shtml) 2018.

43. Berry RJ, Crider KS, Yeargin-Allsopp M. Periconceptional folic acid and risk of autism spectrum disorders. JAMA 2013;309:611-3. [PubMed abstract

(https://www.ncbi.nlm.nih.gov/pubmed/23403688?dopt=Abstract)]

44. Bjork M, Riedel B, Spigset O, et al. Association of folic acid supplementation during pregnancy with the risk of autistic traits in children exposed to antiepileptic drugs in utero. JAMA Neurol 2018;75:160-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29279889?dopt=Abstract)]

45. Schmidt RJ, Kogan V, Shelton JF, et al. Combined prenatal pesticide exposure and folic acid intake in relation to autism spectrum disorder. Environ Health Perspect 2017;125:097007. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28934093?dopt=Abstract)]

46. Goodrich AJ, Volk HE, Tancredi DJ, et al. Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. Autism Res 2018;11:69-80. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29120534?dopt=Abstract)]

47. Roffman JL. Neuroprotective effects of prenatal folic acid supplementation: why timing matters. JAMA Psychiatry 2018;75:747-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29801055?dopt=Abstract)]

48. Caffrey A, Irwin RE, McNulty H, et al. Gene-specific DNA methylation in newborns in response to folic acid supplementation during the second and third trimesters of pregnancy: epigenetic analysis from a randomized controlled trial. Am J Clin Nutr 2018;107:566-75. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29635492?dopt=Abstract)]

49. DeVilbiss EA, Gardner RM, Newschaffer CJ, et al. Maternal folate status as a risk factor for autism spectrum disorders: a review of existing evidence. Br J Nutr 2015;114:663-72. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/26243379?dopt=Abstract)]

50. Suren P, Roth C, Bresnahan M, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. JAMA 2013;309:570-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23403681?dopt=Abstract)]

51. Schmidt RJ, Tancredi DJ, Ozonoff S, et al. Maternal periconceptional folic acid intake and risk of autism spectrum disorders and developmental delay in the CHARGE (CHildhood Autism Risks from Genetics and Environment) case-control study. Am J Clin Nutr 2012;96:80-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22648721?dopt=Abstract)]

52. Levine SZ, Kodesh A, Viktorin A, et al. Association of maternal use of folic acid and multivitamin supplements in the periods before and during pregnancy with the risk of autism spectrum disorder in offspring. JAMA Psychiatry 2018;75:176-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29299606?dopt=Abstract)]

53. Virk J, Liew Z, Olsen J, et al. Preconceptional and prenatal supplementary folic acid and multivitamin intake and autism spectrum disorders. Autism 2016;20:710-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/26408631?dopt=Abstract)]

54. He H, Shui B. Folate intake and risk of bladder cancer: a meta-analysis of epidemiological studies. Int J Food Sci Nutr 2014;65:286-92. [PubMed abstract

(https://www.ncbi.nlm.nih.gov/pubmed/24328495?dopt=Abstract)]

55. Kim YI. Will mandatory folic acid fortification prevent or promote cancer? Am J Clin Nutr 2004;80:1123-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/15531657?dopt=Abstract)]

56. Kim YI. Folate and carcinogenesis: evidence, mechanisms, and implications. J Nutr Biochem 1999;10:66-88. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/15539274?dopt=Abstract)]

57. Kim YI. Folate and cancer: a tale of Dr. Jekyll and Mr. Hyde? Am J Clin Nutr 2018;107:139-42. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29529163?dopt=Abstract)]

58. Andreeva VA, Touvier M, Kesse-Guyot E, et al. B vitamin and/or omega-3 fatty acid supplementation and cancer: ancillary findings from the supplementation with folate, vitamins B6 and B12, and/or omega-3 fatty acids (SU.FOL.OM3) randomized trial. Arch Intern Med 2012;172:540-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22331983?dopt=Abstract)]

59. Ebbing M, Bonaa KH, Nygard O, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. JAMA 2009;302:2119-26. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19920236?dopt=Abstract)]

60. Mason JB. Unraveling the complex relationship between folate and cancer risk. Biofactors 2011;37:253-60. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21915934?dopt=Abstract)]

61. Giovannucci E, Stampfer MJ, Colditz GA, et al. Folate, methionine, and alcohol intake and risk of colorectal adenoma. J Natl Cancer Inst 1993;85:875-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/8492316?dopt=Abstract)]

62. Gibson TM, Weinstein SJ, Pfeiffer RM, et al. Pre- and postfortification intake of folate and risk of colorectal cancer in a large prospective cohort study in the United States. Am J Clin Nutr 2011;94:1053-62. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21813806?dopt=Abstract)]

63. Sanjoaquin MA, Allen N, Couto E, et al. Folate intake and colorectal cancer risk: a meta-analytical approach. Int J Cancer 2005;113:825-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/15499620?dopt=Abstract)]

64. Kennedy DA, Stern SJ, Moretti M, et al. Folate intake and the risk of colorectal cancer: a systematic review and meta-analysis. Cancer Epidemiol 2011;35:2-10. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21177150?dopt=Abstract)]

65. Bassett JK, Severi G, Hodge AM, et al. Dietary intake of B vitamins and methionine and colorectal cancer risk. Nutr Cancer 2013;65:659-67. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23859033?dopt=Abstract)]

66. de Vogel S, Dindore V, van Engeland M, et al. Dietary folate, methionine, riboflavin, and vitamin B-6 and risk of sporadic colorectal cancer. J Nutr 2008;138:2372-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19022960?dopt=Abstract)]

67. Neuhouser ML, Cheng TY, Beresford SA, et al. Red blood cell folate and plasma folate are not associated with risk of incident colorectal cancer in the Women's Health Initiative observational study. Int J Cancer 2015;137:930-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25643945?dopt=Abstract)]

68. Chuang SC, Rota M, Gunter MJ, et al. Quantifying the dose-response relationship between circulating folate concentrations and colorectal cancer in cohort studies: a meta-analysis based on a flexible meta-regression model. Am J Epidemiol 2013;178:1028-37. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23863758?dopt=Abstract)]

69. Song Y, Manson JE, Lee IM, et al. Effect of combined folic acid, vitamin B(6), and vitamin B(12) on colorectal adenoma. J Natl Cancer Inst 2012;104:1562-75. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23066166?dopt=Abstract)]

70. Figueiredo JC, Mott LA, Giovannucci E, et al. Folic acid and prevention of colorectal adenomas: a combined analysis of randomized clinical trials. Int J Cancer 2011;129:192-203. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21170989?dopt=Abstract)]

71. Cole BF, Baron JA, Sandler RS, et al. Folic acid for the prevention of colorectal adenomas: a randomized clinical trial. JAMA 2007;297:2351-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17551129?dopt=Abstract)]

72. Vollset SE, Clarke R, Lewington S, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. Lancet 2013;381:1029-36. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23352552?dopt=Abstract)]

73. van Wijngaarden JP, Swart KM, Enneman AW, et al. Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr 2014;100:1578-86. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25411293?dopt=Abstract)]

74. Tu H, Dinney CP, Ye Y, et al. Is folic acid safe for non-muscle-invasive bladder cancer patients? An evidence-based cohort study. Am J Clin Nutr 2018;107:208-16. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29529165?dopt=Abstract)]

75. Kim SJ, Zuchniak A, Sohn KJ, et al. Plasma folate, vitamin B-6, and vitamin B-12 and breast cancer risk in BRCA1- and BRCA2-mutation carriers: a prospective study. Am J Clin Nutr 2016;104:671-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27465373?dopt=Abstract)]

76. Figueiredo JC, Grau MV, Haile RW, et al. Folic acid and risk of prostate cancer: results from a randomized clinical trial. J Natl Cancer Inst 2009;101:432-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19276452?dopt=Abstract)]

77. Tomaszewski JJ, Cummings JL, Parwani AV, et al. Increased cancer cell proliferation in prostate cancer patients with high levels of serum folate. Prostate 2011;71:1287-93. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21308713?dopt=Abstract)]

78. Wien TN, Pike E, Wisloff T, et al. Cancer risk with folic acid supplements: a systematic review and meta-analysis. BMJ Open 2012;2:e000653. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22240654?dopt=Abstract)]

79. Kim S, Choi BY, Nam JH, et al. Cognitive impairment is associated with elevated serum homocysteine levels among older adults. Eur J Nutr 2018. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29322314?dopt=Abstract)]

80. Kim YI. Folate: a magic bullet or a double edged sword for colorectal cancer prevention? Gut 2006;55:1387-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16966698?dopt=Abstract)]

81. Ulrich CM, Potter JD. Folate supplementation: too much of a good thing? Cancer Epidemiol Biomarkers Prev 2006;15:189-93. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16492904?dopt=Abstract)]

82. Mason JB, Tang SY. Folate status and colorectal cancer risk: a 2016 update. Mol Aspects Med 2017;53:73-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27890600?dopt=Abstract)]

83. Lee JE, Willett WC, Fuchs CS, et al. Folate intake and risk of colorectal cancer and adenoma: modification by time. Am J Clin Nutr 2011;93:817-25. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21270374?dopt=Abstract)]

84. National Toxicology Program. NTP monograph: identifying research needs for assessing safe use of high intakes of folic acid. (https://ntp.niehs.nih.gov/ntp/ohat/folicacid/final_monograph_508.pdf) National Toxicology Program, 2015.

85. Clarke R, Halsey J, Lewington S, et al. Effects of lowering homocysteine levels with B vitamins on cardiovascular disease, cancer, and cause-specific mortality: Meta-analysis of 8 randomized trials involving 37 485 individuals. Arch Intern Med 2010;170:1622-31. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20937919?dopt=Abstract)]

86. Huang T, Chen Y, Yang B, et al. Meta-analysis of B vitamin supplementation on plasma homocysteine, cardiovascular and all-cause mortality. Clin Nutr 2012;31:448-54. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22652362?dopt=Abstract)]

87. Toole JF, Malinow MR, Chambless LE, 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 (https://www.ncbi.nlm.nih.gov/pubmed/14762035?dopt=Abstract)]

88. Lonn E, Yusuf S, Arnold MJ, et al. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med 2006;354:1567-77. [PubMed abstract

(https://www.ncbi.nlm.nih.gov/pubmed/16531613?dopt=Abstract)]

89. Albert CM, Cook NR, Gaziano JM, 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 (https://www.ncbi.nlm.nih.gov/pubmed/18460663?dopt=Abstract)]

90. Ebbing M, Bleie O, Ueland PM, 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 (https://www.ncbi.nlm.nih.gov/pubmed/18714059?dopt=Abstract)]

91. Christen WG, Cook NR, Van Denburgh M, et al. Effect of combined treatment with folic acid, vitamin B6, and vitamin B12 on plasma biomarkers of inflammation and endothelial dysfunction in women. J Am Heart Assoc 2018;7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29776960?dopt=Abstract)]

92. Huo Y, Li J, Qin X, et al. Efficacy of folic acid therapy in primary prevention of stroke among adults with hypertension in China: the CSPPT randomized clinical trial. JAMA 2015;313:1325-35. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25771069?dopt=Abstract)]

93. Study of the Effectiveness of Additional Reductions in Cholesterol Homocysteine Collaborative Group, Armitage JM, Bowman L, et al. Effects of homocysteine-lowering with folic acid plus vitamin B12 vs placebo on mortality and major morbidity in myocardial infarction survivors: a randomized trial. JAMA 2010;303:2486-94. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20571015?dopt=Abstract)]

94. Huo Y, Qin X, Wang J, et al. Efficacy of folic acid supplementation in stroke prevention: new insight from a meta-analysis. Int J Clin Pract 2012;66:544-51. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22607506?dopt=Abstract)]

95. Kong X, Huang X, Zhao M, et al. Platelet count affects efficacy of folic acid in preventing first stroke. J Am Coll Cardiol 2018;71:2136-46. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29747834?dopt=Abstract)]

96. Stampfer M, Willett W. Folate supplements for stroke prevention: targeted trial trumps the rest. JAMA 2015;313:1321-2. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25770867?dopt=Abstract)]

97. Marti-Carvajal AJ, Sola I, Lathyris D, et al. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev 2017;8:CD006612. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25590290?dopt=Abstract)]

98. Jenkins DJA, Spence JD, Giovannucci EL, et al. Supplemental Vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29852980?dopt=Abstract)]

99. Tian T, Yang KQ, Cui JG, et al. Folic acid supplementation for stroke prevention in patients with cardiovascular disease. Am J Med Sci 2017;354:379-87. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29078842?dopt=Abstract)]

100. Seshadri S, Beiser A, Selhub J, et al. Plasma homocysteine as a risk factor for dementia and Alzheimer's disease. N Engl J Med 2002;346:476-83. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/11844848?dopt=Abstract)]

101. Ravaglia G, Forti P, Maioli F, et al. Homocysteine and folate as risk factors for dementia and Alzheimer disease. Am J Clin Nutr 2005;82:636-43. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16155278?dopt=Abstract)]

102. Clarke R. B-vitamins and prevention of dementia. Proc Nutr Soc 2008;67:75-81. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18234134?dopt=Abstract)]

103. Smith AD, Refsum H. Homocysteine, B vitamins, and cognitive impairment. Annu Rev Nutr 2016;36:211-39. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27431367?dopt=Abstract)]

104. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and dementia: an international consensus statement. J Alzheimers Dis 2018;62:561-70. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29480200?dopt=Abstract)]

105. Hooshmand B, Solomon A, Kareholt I, et al. Associations between serum homocysteine, holotranscobalamin, folate and cognition in the elderly: a longitudinal study. J Intern Med 2012;271:204-12. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22077644?dopt=Abstract)]

106. Eussen SJ, de Groot LC, Joosten LW, 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 (https://www.ncbi.nlm.nih.gov/pubmed/16895884?dopt=Abstract)]

107. van der Zwaluw NL, Dhonukshe-Rutten RA, van Wijngaarden JP, et al. Results of 2-year vitamin B treatment on cognitive performance: secondary data from an RCT. Neurology 2014;83:2158-66. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25391305?dopt=Abstract)]

108. Kang JH, Cook N, Manson J, et al. 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 (https://www.ncbi.nlm.nih.gov/pubmed/19064521?dopt=Abstract)]

109. Aisen PS, Schneider LS, Sano M, et al. High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA 2008;300:1774-83. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18854539?dopt=Abstract)]

110. Walker JG, Batterham PJ, Mackinnon AJ, et al. Oral folic acid and vitamin B-12 supplementation to prevent cognitive decline in community-dwelling older adults with depressive symptoms--the

Beyond Ageing Project: a randomized controlled trial. Am J Clin Nutr 2012;95:194-203. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22170358?dopt=Abstract)]

111. Clarke R, Bennett D, Parish S, et al. Effects of homocysteine lowering with B vitamins on cognitive aging: meta-analysis of 11 trials with cognitive data on 22,000 individuals. Am J Clin Nutr 2014;100:657-66. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/24965307?dopt=Abstract)]

112. Balk EM, Raman G, Tatsioni A, et al. Vitamin B6, B12, and folic acid supplementation and cognitive function: a systematic review of randomized trials. Arch Intern Med 2007;167:21-30. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17210874?dopt=Abstract)]

113. Malouf R, Grimley Evans J. Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. Cochrane Database Syst Rev 2008:CD004514. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18843658?dopt=Abstract)]

114. Dangour AD, Whitehouse PJ, Rafferty K, et al. B-vitamins and fatty acids in the prevention and treatment of Alzheimer's disease and dementia: a systematic review. J Alzheimers Dis 2010;22:205-24. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20847412?dopt=Abstract)]

115. Ford AH, Almeida OP. Effect of homocysteine lowering treatment on cognitive function: a systematic review and meta-analysis of randomized controlled trials. J Alzheimers Dis 2012;29:133-49. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22232016?dopt=Abstract)]

116. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007;369:208-16. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17240287?dopt=Abstract)]

117. Huang X, Fan Y, Han X, et al. Association between serum vitamin levels and depression in U.S. adults 20 years or older based on National Health and Nutrition Examination Survey 2005-2006. Int J Environ Res Public Health 2018;15. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29890739?dopt=Abstract)]

118. Gougeon L, Payette H, Morais JA, et al. Intakes of folate, vitamin B6 and B12 and risk of depression in community-dwelling older adults: the Quebec Longitudinal Study on Nutrition and Aging. Eur J Clin Nutr 2016;70:380-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/26648330?dopt=Abstract)]

119. Morris MS, Fava M, Jacques PF, et al. Depression and folate status in the US population. Psychother Psychosom 2003;72:80-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/12601225?dopt=Abstract)]

120. Papakostas GI, Petersen T, Mischoulon D, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. J Clin Psychiatry 2004;65:1090-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/15323594?dopt=Abstract)]

121. Trujillo J, Vieira MC, Lepsch J, et al. A systematic review of the associations between maternal nutritional biomarkers and depression and/or anxiety during pregnancy and postpartum. J Affect Disord 2018;232:185-203. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29494902?dopt=Abstract)]

122. Chong MF, Wong JX, Colega M, et al. Relationships of maternal folate and vitamin B12 status during pregnancy with perinatal depression: The GUSTO study. J Psychiatr Res 2014;55:110-6. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/24774647?dopt=Abstract)]

123. Blunden CH, Inskip HM, Robinson SM, et al. Postpartum depressive symptoms: the B-vitamin link. Ment Health Fam Med 2012;9:5-13. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23277793?dopt=Abstract)]

124. Yan J, Liu Y, Cao L, et al. Association between duration of folic acid supplementation during pregnancy and risk of postpartum depression. Nutrients 2017;9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29099069?dopt=Abstract)]

125. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. J Affect Disord 2000;60:121-30. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/10967371?dopt=Abstract)]

126. Bedson E, Bell D, Carr D, et al. Folate Augmentation of Treatment--Evaluation for Depression (FolATED): randomised trial and economic evaluation. Health Technol Assess 2014;18:vii-viii, 1-159. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25052890?dopt=Abstract)]

127. Roberts E, Carter B, Young AH. Caveat emptor: Folate in unipolar depressive illness, a systematic review and meta-analysis. J Psychopharmacol 2018;32:377-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29442609?dopt=Abstract)]

128. Sarris J, Murphy J, Mischoulon D, et al. Adjunctive nutraceuticals for depression: A systematic review and meta-analyses. Am J Psychiatry 2016;173:575-87. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27113121?dopt=Abstract)]

129. Cleare A, Pariante CM, Young AH, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. J Psychopharmacol 2015;29:459-525. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25969470?dopt=Abstract)]

130. Ravindran AV, Balneaves LG, Faulkner G, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 5. Complementary and Alternative medicine treatments. Can J Psychiatry 2016;61:576-87. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27486153?dopt=Abstract)]

131. Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double-blind, parallel-sequential trials. Am

J Psychiatry 2012;169:1267-74. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23212058?dopt=Abstract)]

132. Wilson RD, Genetics C, Motherisk. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can 2007;29:1003-13. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18053387?dopt=Abstract)]

133. Pitkin RM. Folate and neural tube defects. Am J Clin Nutr 2007;85:285S-8S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17209211?dopt=Abstract)]

134. Williams J, Mai CT, Mulinare J, et al. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995-2011. MMWR Morb Mortal Wkly Rep 2015;64:1-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25590678?dopt=Abstract)]

135. Lamers Y. Folate recommendations for pregnancy, lactation, and infancy. Ann Nutr Metab 2011;59:32-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22123635?dopt=Abstract)]

136. Scott JM. Evidence of folic acid and folate in the prevention of neural tube defects. Bibl Nutr Dieta 2001:192-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/11125577?dopt=Abstract)]

137. Molloy AM, Kirke PN, Brody LC, et al. Effects of folate and vitamin B12 deficiencies during pregnancy on fetal, infant, and child development. Food Nutr Bull 2008;29:S101-11; discussion S12-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18709885?dopt=Abstract)]

138. Williams LJ, Rasmussen SA, Flores A, et al. Decline in the prevalence of spina bifida and anencephaly by race/ethnicity: 1995-2002. Pediatrics 2005;116:580-6. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16140696?dopt=Abstract)]

139. Rader JI, Schneeman BO. Prevalence of neural tube defects, folate status, and folate fortification of enriched cereal-grain products in the United States. Pediatrics 2006;117:1394-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16585338?dopt=Abstract)]

140. Dary O. Nutritional interpretation of folic acid interventions. Nutr Rev 2009;67:235-44. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19335717?dopt=Abstract)]

141. Shane B. Folate-responsive birth defects: of mice and women. Am J Clin Nutr 2012;95:1-2. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/22158725?dopt=Abstract)]

142. Viswanathan M, Treiman KA, Kish-Doto J, et al. Folic acid supplementation for the prevention of neural tube defects: an updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2017;317:190-203. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28097361?dopt=Abstract)]

143. Centers for Disease Control and Prevention. Use of folic acid for prevention of spina bifida and other neural tube defects--1983-1991. MMWR Morb Mortal Wkly Rep 1991;40:513-6. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/2072886?dopt=Abstract)]

144. Czeizel AE, Puho EH, Langmar Z, et al. Possible association of folic acid supplementation during pregnancy with reduction of preterm birth: a population-based study. Eur J Obstet Gynecol Reprod Biol 2010;148:135-40. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19926391?dopt=Abstract)]

145. Liu S, Joseph KS, Luo W, et al. Effect of folic acid food fortification in Canada on congenital heart disease subtypes. Circulation 2016;134:647-55. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/27572879?dopt=Abstract)]

146. Botto LD, Mulinare J, Erickson JD. Occurrence of congenital heart defects in relation to maternal mulitivitamin use. Am J Epidemiol 2000;151:878-84. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/10791560?dopt=Abstract)]

147. Shaw GM, O'Malley CD, Wasserman CR, et al. Maternal periconceptional use of multivitamins and reduced risk for conotruncal heart defects and limb deficiencies among offspring. Am J Med Genet 1995;59:536-45. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/8585581?dopt=Abstract)]

148. Johnson MA. If high folic acid aggravates vitamin B12 deficiency what should be done about it? Nutr Rev 2007;65:451-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17972439?dopt=Abstract)]

149. Morris MS, Jacques PF, Rosenberg IH,et al. Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;85:193-200. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17209196?dopt=Abstract)]

150. Selhub J, Morris MS, Jacques PF. In vitamin B12 deficiency, higher serum folate is associated with increased total homocysteine and methylmalonic acid concentrations. Proc Natl Acad Sci U S A 2007;104:19995-20000. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/18056804?dopt=Abstract)]

151. Selhub J, Morris MS, Jacques PF, et al. Folate-vitamin B-12 interaction in relation to cognitive impairment, anemia, and biochemical indicators of vitamin B-12 deficiency. Am J Clin Nutr 2009;89:702S-6S. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19141696?dopt=Abstract)]

152. Berry RJ, Carter HK, Yang Q. Cognitive impairment in older Americans in the age of folic acid fortification. Am J Clin Nutr 2007;86:265-7; author reply 7-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17616791?dopt=Abstract)]

153. Carmel R. Does high folic acid intake affect unrecognized cobalamin deficiency, and how will we know it if we see it? Am J Clin Nutr 2009;90:1449-50. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/19889828?dopt=Abstract)]

154. Valera-Gran D, Navarrete-Munoz EM, Garcia de la Hera M, Fernandez-Somoano A, Tardon A, Ibarluzea J, et al. Effect of maternal high dosages of folic acid supplements on neurocognitive

development in children at 4-5 y of age: the prospective birth cohort Infancia y Medio Ambiente (INMA) study. Am J Clin Nutr 2017;106:878-87. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28724645?dopt=Abstract)]

155. Troen AM, Mitchell B, Sorensen B, et al. Unmetabolized folic acid in plasma is associated with reduced natural killer cell cytotoxicity among postmenopausal women. J Nutr 2006;136:189-94. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16365081?dopt=Abstract)]

156. Morris MS, Jacques PF, Rosenberg IH, Selhub J. Circulating unbetabolied folic acid and 5-methyltetrahydrofolate in relation to anemia, macrocytosis, and cognitive test performance in American seniors. Am J Clin Nutr. 2010 Jun;91(6):1733-44. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20357042?dopt=Abstract)]

157. Pfeiffer CM, Sternberg MR, Fazili Z, et al. Unmetabolized folic acid is detected in nearly all serum samples from US children, adolescents, and adults. J Nutr 2015;145:520-31. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/25733468?dopt=Abstract)]

158. Stamm RA, March KM, Karakochuk CD, et al. Lactating Canadian women consuming 1000 µg folic acid daily have high circulating serum folic acid above a threshold concentration of serum total folate. J Nutr 2018;148:1103-8. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/29901753?dopt=Abstract)]

159. Page R, Robichaud A, Arbuckle TE, et al. Total folate and unmetabolized folic acid in the breast milk of a cross-section of Canadian women. Am J Clin Nutr 2017;105:1101-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/28298392?dopt=Abstract)]

160. Obeid R, Kasoha M, Kirsch SH, et al. Concentrations of unmetabolized folic acid and primary folate forms in pregnant women at delivery and in umbilical cord blood. Am J Clin Nutr 2010;92:1416-22. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/20844072?dopt=Abstract)]

161. Plumptre L, Masih SP, Ly A, et al. High concentrations of folate and unmetabolized folic acid in a cohort of pregnant Canadian women and umbilical cord blood. Am J Clin Nutr 2015;102:848-57. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/26269367?dopt=Abstract)]

162. Sweeney MR, McPartlin J, Scott J. Folic acid fortification and public health: report on threshold doses above which unmetabolised folic acid appear in serum. BMC Public Health 2007;7:41. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/17378936?dopt=Abstract)]

163. Kelly P, McPartlin J, Goggins M, et al. Unmetabolized folic acid in serum: acute studies in subjects consuming fortified food and supplements. Am J Clin Nutr 1997;65:1790-5. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/9174474?dopt=Abstract)]

164. Sweeney MR, McPartlin J, Weir DG, et al. Postprandial serum folic acid response to multiple doses of folic acid in fortified bread. Br J Nutr 2006;95:145-51. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/16441927?dopt=Abstract)]

165. U.S. Food and Drug Administration. Guidance for Industry: A Food Labeling Guide (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-food-labeling-guide)(14. Appendix F: Calculate the Percent Daily Value for the Appropriate Nutrients). 2013.

166. Natural Medicines. Folate. (https://naturalmedicines.therapeuticresearch.com) 2018.

167. Duhra P. Treatment of gastrointestinal symptoms associated with methotrexate therapy for psoriasis. J Am Acad Dermatol 1993;28:466-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/8445064?dopt=Abstract)]

168. Ortiz Z, Shea B, Suarez Almazor M, et al. Folic acid and folinic acid for reducing side effects in patients receiving methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2000:CD000951. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/23728635?dopt=Abstract)]

169. Linnebank M, Moskau S, Semmler A, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. Ann Neurol 2011;69:352-9. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/21246600?dopt=Abstract)]

170. Halsted CH, Gandhi G, Tamura T. Sulfasalazine inhibits the absorption of folates in ulcerative colitis. N Engl J Med 1981;305:1513-7. [PubMed abstract (https://www.ncbi.nlm.nih.gov/pubmed/6117796?dopt=Abstract)]

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