

Folic Acid Supplementation for the Prevention of Neural Tube Defects

An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

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IMPORTANCE Neural tube defects are among the most common congenital anomalies in the United States. Periconceptional folic acid supplementation is a primary care-relevant preventive intervention.

OBJECTIVE To review the evidence on folic acid supplementation for preventing neural tube defects to inform the US Preventive Services Task Force for an updated Recommendation Statement.

DATA SOURCES MEDLINE, Cochrane Library, EMBASE, and trial registries through January 28, 2016, with ongoing surveillance through November 11, 2016; references; experts.

STUDY SELECTION English-language studies of folic acid supplementation in women. Excluded were poor-quality studies; studies of prepubertal girls, men, women without the potential for childbearing, and neural tube defect recurrence; and studies conducted in developing countries.

DATA EXTRACTION AND SYNTHESIS Two investigators independently reviewed abstracts, full-text articles, and risk of bias of included studies. One investigator extracted data and a second checked accuracy. Because of heterogeneity, data were not pooled.

MAIN OUTCOMES AND MEASURES Neural tube defects, harms of treatment (twinning, respiratory outcomes).

RESULTS A total of 24 studies (N > 58 860) were included. In 1 randomized clinical trial from Hungary initiated in 1984, incidence of neural tube defects for folic acid supplementation compared with trace element supplementation was 0% vs 0.25% (Peto odds ratio [OR], 0.13 [95% CI, 0.03-0.65]; n = 4862). Odds ratios from cohort studies recruiting participants between 1984 and 1996 demonstrated beneficial associations and ranged from 0.11 to 0.27 (n = 19 982). Three of 4 case-control studies with data from 1976 through 1998 reported ORs ranging from 0.6 to 0.7 (n > 7121). Evidence of benefit led to food fortification in the United States beginning in 1998, after which no new prospective studies have been conducted. More recent case-control studies drawing from data collected after 1998 have not demonstrated a protective association consistently with folic acid supplementation, with ORs ranging from 0.93 to 1.4 and confidence intervals spanning the null (n > 13 990). Regarding harms, 1 trial (OR, 1.40 [95% CI, 0.89-2.21]; n = 4767) and 1 cohort study (OR, 1.04 [95% CI, 0.91-1.18]; n = 2620) found no statistically significant increased risk of twinning. Three systematic reviews found no consistent evidence of increased risk of asthma (OR, 1.06 [95% CI, 0.99-1.14]; n = 14 438), wheezing, or allergy.

CONCLUSIONS AND RELEVANCE In studies conducted before the initiation of food fortification in the United States in 1998, folic acid supplementation provided protection against neural tube defects. Newer postfortification studies have not demonstrated a protective association but have the potential for misclassification and recall bias, which can attenuate the measured association of folic acid supplementation with neural tube defects.

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Neural tube defects (NTDs) are among the most common congenital anomalies in the United States. NTDs occur very early in the pregnancy, with limited or no chance for complete recovery. The Centers for Disease Control and Prevention estimated that the average annual prevalence of the 2 most common kinds of NTDs, anencephaly and spina bifida, was 6.5 per 10 000 live births for the period from 2009 to 2011.¹ Prevention is an important medical intervention. Periconceptional folic acid supplementation is a primary prevention intervention that can be implemented in primary care settings.

In 2009, the US Preventive Services Task Force (USPSTF) recommended that all women planning a pregnancy or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg of folic acid (A recommendation). To inform an updated recommendation, the evidence on benefits and harms of folic acid supplementation in populations relevant to US primary care was reviewed.

Methods

Scope of the Review

Detailed methods and contextual information (on current intake of folic acid from diet and other sources, effect of folic acid outside the periconceptional period, variation in benefits by risk factors, and supplementation benefits other than protection against neural tube defects) are available in the full evidence report available at <https://www.uspreventiveservicestaskforce.org/Page/Document/final-evidence-review146/folic-acid-for-the-prevention-of-neural-tube-defects-preventive-medication>. Figure 1 shows the analytic framework and key questions (KQs) that guided the review.

Data Sources and Searches

We searched PubMed, the Cochrane Library, and EMBASE for English-language articles published from database inception through January 28, 2016. The search strategies for these

databases are listed in the eMethods in the Supplement. Unpublished literature was searched for in ClinicalTrials.gov, HSRProj (Health Services Research Projects in Progress), the World Health Organization's International Clinical Trials Registry Platform, and NIH Reporter. To supplement electronic searches, the reference lists of pertinent articles and all suggested citations from peer reviewers were reviewed. Ongoing surveillance was conducted after January 2016 through article alerts and targeted searches of high-impact journals to identify major studies published in the interim that may affect the conclusions or understanding of the evidence and therefore the related USPSTF recommendation. The last surveillance was conducted on November 11, 2016.

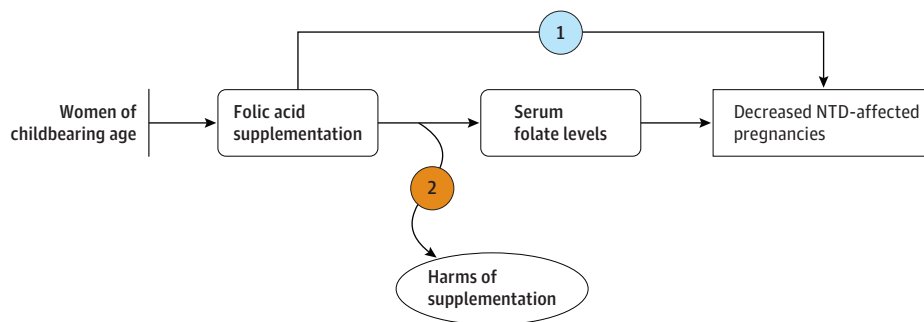
Study Selection

Two investigators independently reviewed titles, abstracts, and full-text articles using prespecified inclusion criteria for each KQ (eTable 1 in the Supplement).

Studies were included if they focused on the use of folic acid supplementation for the prevention of NTD-affected pregnancies in women of childbearing age. Not included were studies of prepubertal girls or men or women without the potential for childbearing (eg, postmenopausal, genetic, uterine, or ovarian abnormalities). We searched for studies that examined the use of folic acid supplementation with or without food fortification or naturally occurring folate for the prevention of NTDs. We also searched for studies that examined the supplementation of micronutrients (eg, multivitamin, iron) in combination with folic acid for the prevention of NTDs. For all KQs, we searched for studies conducted in the United States or in countries rated "very high" on the United Nations Human Development Index.³

Studies were included that compared interventions with placebo, no treatment, dietary supplementation only, supplementation with prenatal vitamins without folic acid, or iron supplements without folic acid for questions on benefits and harms and variations in subpopulations (KQs 1a, 1b, and 2a). Included studies

Figure 1. Analytic Framework and Key Questions



Key questions

- 1
 - a. To what extent does folic acid supplementation reduce the risk for neural tube defects (NTDs) (first occurrence) in women of childbearing age?
 - b. Does the effect of folic acid supplementation on NTDs (first occurrence) differ by race or ethnicity?
 - c. Do the benefits of folic acid supplementation differ by dosage, timing, or duration of therapy?
- 2
 - a. Are there harms associated with folic acid supplementation to the mother, fetus, neonate, or child?
 - b. Do the harms of folic acid supplementation differ by dosage, timing, or duration of therapy?

This analytic framework uses USPSTF iconography and convention.² Arrows represent linkages in the evidence chain. Health outcomes are represented by rectangles with squared corners and intermediate outcomes by rectangles with rounded corners. Curved arrows lead to ovals representing harms.

compared interventions with lower or higher dose of folic acid supplementation only for questions about variations in benefits and harms by dosage (KQs 1b, 1c, and 2b).

Studies were sought that reported on the benefits of folic acid supplementation initiated before the index pregnancy or in the first trimester to prevent NTDs for questions on benefits and variation in benefits in subpopulations (KQs 1a and 1b). The timing of the intervention was expanded through the end of the pregnancy for questions on the effect of timing on benefits or any harms questions (KQs 1c, 2a, and 2b).

For benefits and harms (KQs 1 and 2), randomized clinical trials (RCTs), nonrandomized controlled trials, cohort studies, case-control studies, and systematic reviews were included. Additionally, for harms (KQs 2a and 2b), registry data were included.

Two reviewers dually reviewed the quality of all studies included in the 2009 report that met the inclusion criteria for the current review and resolved disagreement by discussion and consensus.

Data Extraction and Quality Assessment

For each included study, one investigator extracted information about methods, patient population, intervention, comparator, outcomes, timing, setting, and study design, and a second investigator reviewed for completeness and accuracy. Two independent investigators assessed the quality of each study as good, fair, or poor, using predefined criteria developed by the USPSTF and adapted for this topic (eTables 2, 3, 4, and 5 in the [Supplement](#)).

Disagreements were resolved by discussion and consensus. Issues leading to a judgment of poor quality included the risk of misclassification bias from retrospective recall of level and timing of exposure; the risk of selection bias from not identifying all cases of the outcome, including fetal deaths; and the risk of confounding from not appropriately accounting for factors such as infertility that might influence both exposure to folic acid supplementation and the outcome of twinning. Studies with 1 or more of these features were rated as poor quality. Other flaws that resulted in poor-quality ratings included initially assembled groups not close to being comparable or maintained throughout the study (including overall attrition of at least 20% or differential attrition of at least 15% between groups); use of unreliable or invalid measurement instruments or unequal application among groups (including not masking outcome assessment); and, for RCTs, the lack of intention-to-treat analysis.

Data Synthesis and Analysis

Findings for each KQ were qualitatively synthesized by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, the clinical and methodological heterogeneity (in population, interventions, and outcomes) of the studies were assessed following established guidance.⁴

Results

A total of 5786 titles and abstracts and 757 full-text articles were screened (Figure 2). Of the 32 good- or fair-quality articles on primary studies or systematic reviews, 20⁵⁻²⁴ addressed KQ1a, 3^{6,7,20} addressed KQ1b, 8^{6,7,17-22} addressed KQ1c, 20^{8-13,15,23-35} addressed

KQ2a, and 6^{25-27,33,35,36} addressed KQ2b. Because of the heterogeneity across studies and over time, results were not pooled.

Benefits of Folic Acid Supplementation

Key Question 1a. To what extent does folic acid supplementation reduce the risk for NTDs (first occurrence) in women of childbearing age?

A total of 20 publications were found on the question of benefits of folic acid supplementation. Seven publications present results of the only eligible RCT.^{8-13,15} The study, conducted in Hungary, was an RCT initiated in 1984 and terminated in 1992, with information collected through 1993. Three publications relate to 2 cohort studies; one was a Hungarian cohort study of women recruited between 1993 and 1996,¹⁴ and the second was a cohort drawn from women who underwent α -fetoprotein screening or amniocentesis between 1984 and 1987.^{18,19} All other studies were case-control studies and compared infants having NTD-associated malformations with nonmalformed infants^{5-7,17,20,21} or with infants having non-NTD-associated malformations.^{16,22} Additionally, we checked the previous update to ensure that we had rereviewed and included all previously evaluated studies if they continued to meet inclusion criteria.^{23,24}

These 20 publications, comprising 11 primary studies and 1 systematic review,^{23,24} drew from 8 data sources (Hungarian trial,^{8-13,15} Hungarian cohort,¹⁴ the New England study,^{18,19} the National Birth Defects Prevention Study,^{5,6} the Slone Birth Defects Study,^{7,16,22} the National Institute of Child Health and Human Development (NICHD) Neural Tube Defects Study,¹⁷ the California Birth Defects Monitoring Program,²⁰ and the Texas Department of Health's Neural Tube Defect Project²¹). Together they span births occurring over 3 decades, from 1976 through 2007.

Although the RCT and the cohort studies potentially offer greater controls for potential sources of bias, they predate the 1998 regulations on mandatory food fortification in the United States. The case-control studies span a period ranging from 1976 through 2008, including several relying exclusively on data collected after food fortification. These 8 publications of case-control data draw from related, or in some cases subsets, of the same data.

Because study design, source of data, and secular changes in food fortification over time can all influence interpretation of study findings, results are presented first by study design, second by data source (presenting national or multistate ahead of 2-state or single-state studies), and third by date of data collection for each publication for a data source.

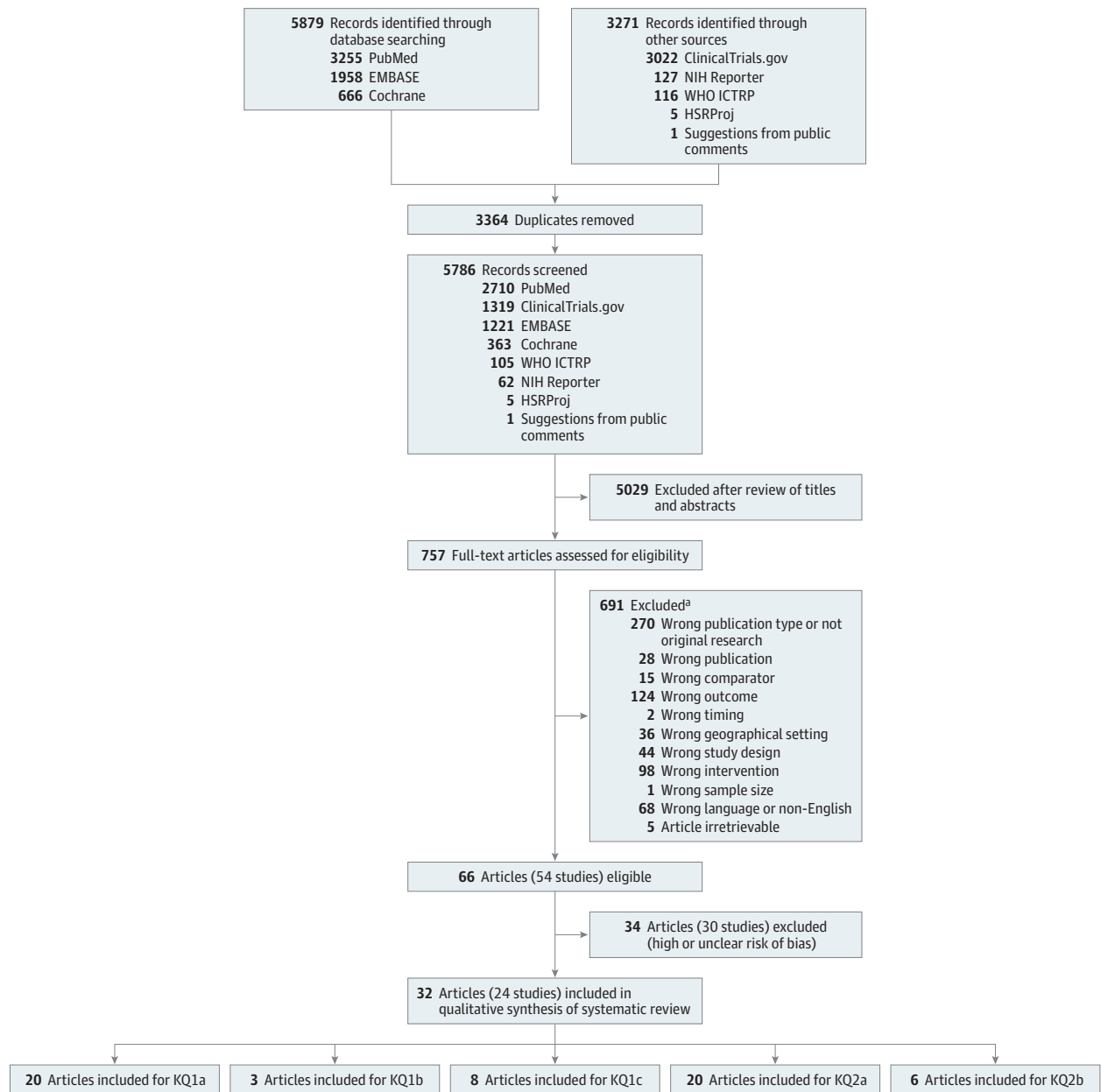
Evidence From Trials

One RCT, described in 7 publications,^{8-13,15} randomized 5453 women in Hungary preconceptionally to a vitamin supplement containing folic acid or a trace-element supplement (Table 1). The trial reported no cases of NTDs in the experimental group and 6 cases in the control group (0% vs 0.25%; 25 fewer cases per 10 000 [95% CI, 3-47 fewer]; $P = .01$ by Fisher exact test; Peto odds ratio [OR], 0.13 [95% CI, 0.03-0.65]).

Evidence From Cohort Studies

At the conclusion of the RCT described above, no additional RCT was considered ethically possible because of the clear benefits of folic acid supplementation. The authors continued their investigation using the same intervention in a cohort of 6112 women drawn

Figure 2. Literature Search Flow Diagram



KQ indicates key question.

^a Reasons for exclusion: Wrong publication type/not original research: Study was not original research or systematic review. Wrong population: Study was not conducted in an eligible population. Wrong comparator: Study did not include eligible comparators or had no comparators. Wrong outcome: Study did not include eligible outcomes or had no outcomes. Wrong timing: Study did not examine supplementation before index pregnancy or during the first

trimester. Wrong geographic setting: Study was not conducted in a country relevant to US practice (very high human development index). Wrong study design: Study did not include an eligible design. Wrong intervention: Study did not include an eligible intervention or had no intervention. Wrong sample size: Study had 50 or fewer participants. Wrong language/non-English: Study was not published in English. Article irretrievable: Study could not be retrieved.

from the Hungarian Periconceptional Service (1993 to 1996), with supplementation provided before conception (Table 1).¹⁴ When compared with outcomes for unsupplemented pregnant women, the adjusted OR of an NTD-affected pregnancy for supplemented women was 0.11 (95% CI, 0.01-0.91; 0% vs 0.29%; 29 fewer cases per 10 000 [95% CI, 9-50 fewer]).¹⁴ A cohort study of 23 491 women in New England undergoing α -fetoprotein screening or

amniocentesis between weeks 15 and 20 of gestation (1984 to 1987) defined exposure as the use of at least 1 multivitamin containing folic acid per week, between weeks 1 and 6 following conception (Table 2). Use of multivitamins containing folic acid was associated with an OR for NTD-affected pregnancy of 0.27 (95% CI, 0.11-0.63; 0.09% vs 0.35%, 26 fewer cases per 10 000 [95% CI, 4-47 fewer]).¹⁸

Table 1. Results of Randomized Clinical Trials and Cohort Studies Examining the Benefits of Folic Acid Supplementation on Neural Tube Defects (Key Question 1)^a

| Source | Study or Database Name | Period of Exposure | Population | Definition of Exposure ^b | Timing of Measurement of Exposure | Outcomes | No. | | | Statistical Adjustments | | |
|------------------------------------|------------------------|--------------------|--|--|---|---|--------------|---------|------------------|-------------------------|------------------|---|
| | | | | | | | Exposed NTDs | No NTDs | Not Exposed NTDs | | | |
| Randomized Clinical Trials | | | | | | | | | | | | |
| Czeizel et al, ⁸ 1992 | Hungarian RCT | 1984-1992 | Women planning a pregnancy without any delayed conception or infertility and not currently pregnant, Hungary | Assigned to daily use of multivitamins containing folic acid for 28 d before conception and at least until the date of the second missed menstrual period ^d | Prospective | Live births, termination in the second trimester following prenatal diagnosis, and stillbirths with NTDs ^e | 0 | 2471 | 6 | 2385 | 0.13 (0.03-0.65) | None |
| Czeizel et al, ⁹ 1993 | | | | | | | | | | | | |
| Czeizel et al, ¹⁰ 1994 | | | | | | | | | | | | |
| Czeizel et al, ¹¹ 1994 | | | | | | | | | | | | |
| Czeizel et al, ¹² 1993 | | | | | | | | | | | | |
| Czeizel et al, ¹⁵ 1996 | | | | | | | | | | | | |
| Czeizel et al, ¹³ 1998 | | | | | | | | | | | | |
| Cohort Studies | | | | | | | | | | | | |
| Czeizel et al, ¹⁴ 2004 | Hungarian cohort | 1993-1996 | Women planning a pregnancy without any delayed conception or infertility and not currently pregnant, Hungary | Use of multivitamins containing folic acid for 28 d before conception and at least until first missed menstrual period (excluding women who conceived before or during the first month of the supplementation, or had missing intake of the supplement for more than 7 d) ^f | Prospective | Live births, terminations in the second or third trimester following prenatal diagnosis, and stillbirths (late fetal death after the 28th week of gestation and/or weighing >1000 g) with NTDs ^g | 0 | 3056 | 9 | 3047 | 0.11 (0.01-0.91) | Birth order (first or second and more), chronic maternal disorder, and history of previous unsuccessful pregnancies including fetal death or congenital abnormalities in fetuses or newborn infants |
| Milunsky et al, ¹⁸ 1989 | NR | 1984-1987 | Women undergoing MSAFP screen or an amniocentesis, United States | Use of multivitamins containing folic acid in wk 1-6 of pregnancy ^h | Retrospective, at 15-20 wk of pregnancy | NTDs, defined as spina bifida, anencephaly, or encephalocele ^h | 10 | 10 703 | 11 | 3146 | 0.27 (0.11-0.63) | None |

Abbreviations: MSAFP, maternal serum α-fetoprotein; NR, not reported; NTD, neural tube defect; OR, odds ratio; USPSTF, US Preventive Services Task Force.

^a Studies were rated as fair quality, based on criteria developed by the USPSTF² and Cochrane methodologists.^{3,7,28}

^b In cohort studies with multiple definitions of exposure, the definition representing or closest to consistent use during the periconceptional period was selected.

^c For the RCT, OR is Peto OR; for cohort studies, OR includes adjusted OR, if reported by the study; if no adjusted OR was reported, OR was calculated.

^d Compared with trace-element supplement.

^e Compared with live births, terminations in the second trimester following prenatal diagnosis, and stillbirths without NTDs.

^f Compared with no supplementation.

^g Compared with live births, terminations in the second trimester following prenatal diagnosis, and stillbirths without NTDs.

^h Compared with no NTD diagnosis (sample limited to women with pregnancy outcome data available).

Table 2. Results of Case-Control Studies Examining the Benefits of Folic Acid Supplementation on Neural Tube Defects (Key Question 1)^{a,b}

| Source | Study or Database Name | Period of Exposure | Population | Definition of Exposure ^c | Timing of Measurement of Exposure | Case Definition | No. Exposed | | OR (95% CI) ^d | Statistical Adjustments |
|--|---|--------------------|---|--|--|---|-------------|---------|--------------------------|--|
| | | | | | | | NTDs | No NTDs | | |
| Case-Control Studies From Multistate Sources | | | | | | | | | | |
| Mosley et al, ⁶ 2008 | National Birth Defects Prevention Study | 1998-2003 | Mothers with and without pregnancies affected by birth defects, United States | Consistent use (at half the days) of any supplement containing folic acid 3 mo before pregnancy through first mo of pregnancy ^e | Retrospective, no earlier than 6 wk and no later than 24 mo after the expected date of delivery ³⁹ | Anencephaly live births, fetal deaths, and elective pregnancy terminations ⁵ Spina bifida live births, fetal deaths, and elective pregnancy terminations ⁵ | 38 | 965 | 1.2 (0.8-1.9) | Maternal race and education |
| Agopian et al, ⁵ 2013 | National Birth Defects Prevention Study | 1997-2007 | Mothers with and without pregnancies affected by birth defects, United States | Folic acid, multivitamin, or prenatal vitamin supplementation in the month before pregnancy through first month of pregnancy ^e | Retrospective, no earlier than 6 weeks and no later than 24 mo after the expected date of delivery ³⁹ | Spina bifida or anencephaly live births, fetal deaths, and elective pregnancy terminations ⁵ | 617 | 4,293 | 0.93 (0.82-1.06) | BMI [≥] 30.0, low dietary folate intake, anticonvulsant medication use, female infant sex, family history of NTDs in a first- or second-degree relative, maternal Hispanic ethnicity ⁹ |
| Werler et al, ²² 1993 | Slope Birth Defects Study | 1988-1991 | Mothers with NTD-affected pregnancies and mothers with pregnancies affected by other major malformations, United States | Daily use of supplements containing folic acid from 28 d before LMP through 28 d after LMP ^e | Retrospective, within 6 mo of delivery | Live-born and stillborn infants and therapeutic abortions with NTDs (anencephaly, spina bifida, or encephalocele) ^h | 34 | 339 | 0.6 (0.4-0.8) | Maternal age, maternal education, annual family income, birth status |
| Hernandez-Diaz et al, ¹⁶ 2001 | Slope Birth Defects Study | 1976-1998 | Mothers of malformed children, United States | Daily folic acid supplementation during the 2 mo after the LMP ^e | Retrospective, within 6 mo of delivery | Live-born and stillborn infants and therapeutic abortions with NTD; stillbirths and therapeutic abortions included from 1988 onward ^h | 140 | 939 | 0.7 (0.5-0.8) | Interview year, region, maternal age, education, weight before pregnancy, and UTIs or other infections early in pregnancy |
| Ahrens et al, ⁷ 2011 | Slope Birth Defects Study | 1998-2008 | Mothers with and without pregnancies affected by birth defects, United States | Folic acid supplementation use \geq 4 d per wk for \geq 8 wk in period from 2 mo before LMP to 1 mo after LMP ⁱ | Retrospective, within 6 mo of delivery | Malformed live-born infants, therapeutic abortions after 12 wk gestation, and fetal deaths after 20 wk gestation ^f | 83 | 2573 | 1.11 (0.74-1.65) | Race, BMI, pregnancy intent, and study center |

(continued)

Table 2. Results of Case-Control Studies Examining the Benefits of Folic Acid Supplementation on Neural Tube Defects (Key Question 1)^{a,b} (continued)

| Source | Study or Database Name | Period of Exposure | Population | Definition of Exposure ^c | Timing of Measurement of Exposure | Case Definition | No. Exposed | | Not Exposed | | OR (95% CI) ^d | Statistical Adjustments |
|----------------------------------|---|--------------------|--|---|---|---|-------------|---------|-------------|---------|--------------------------|--|
| | | | | | | | NTDs | No NTDs | NTDs | No NTDs | | |
| Mills et al, ¹⁷ 1989 | NICHD Neural Tube Defects Study (data from California and Illinois) | 1985-1987 | Mothers with and without pregnancies affected by birth defects, United States | Vitamin supplements containing folic acid (exposure defined taking supplements containing the RDA of at least 4 vitamins or a higher dose at least 6 d per week) ^e | Retrospective, no more than 3 mo after delivery | Mothers of an infant or fetus with an NTD ^f | 86 | 84 | 464 | 456 | 1.00 (0.73-1.40) | None |
| Shaw et al, ²⁰ 1995 | California Birth Defects Monitoring Program | 1989-1991 | Mothers with and without singleton pregnancies affected by reportable birth defects, United States | Any use of vitamin supplements containing folic acid in the 3 mo before conception ^e | Retrospective, average of 5 mo after delivery | Singleton live-born infants and electively terminated fetuses with an NTD (anencephaly, spina bifida cystic, craniorachischisis, and iniencephaly) ^f | 88 | 98 | 207 | 149 | 0.65 (0.45-0.94) | None |
| Suarez et al, ²¹ 2000 | Texas Department of Health's Neural Tube Defect Project | 1995-1999 | Mothers with and without NTD-affected pregnancies, United States | Daily use in every month in the preconception period (≤3 mo before conception) vs no folic acid use ^e | Retrospective, approximately 1 mo postpartum | Infants or fetuses who had anencephaly (including craniorachischisis and iniencephaly), spina bifida, or encephalocele identified at birth or prenatally ^f | 3 | 4 | 66 | 68 | 1.12 (0.22-5.78) | Maternal age, education, obesity, and previous stillbirth or miscarriage |

^dIncludes adjusted OR; if reported by the study; if no adjusted OR was reported, OR was calculated.

^eCompared with no supplementation.

^fCompared with live births only, defined as "normal," "without major birth defects," or "nonmalformed."

^gBMI calculated as weight in kilograms divided by height in meters squared.

^hCompared with malformations other than NTDs or "other major malformations."

ⁱCompared with no or very little use.

Abbreviations: BMI, body mass index; LMP, last menstrual period; NICHD, National Institute of Child Health and Human Development; NTD, neural tube defect; OR, odds ratio; RDA, recommended dietary allowance; USPSTF, US Preventive Services Task Force; UTI, urinary tract infection.

^a Studies are listed by data source first (multistate case-control studies first, single/2-state case-control studies second), then by name of the database or study, and last by the last date of exposure (from oldest to newest).

^b All studies were rated as fair quality, based on criteria developed by the USPSTF² and Cochrane methodologists.^{3,7,38}

^c In studies with multiple definitions of exposure, the definition representing or closest to consistent use during the preconceptional period was selected.

Evidence From Case-Control Studies

Case-control studies included multistate, 2-state, and single-state sources (Table 2). Two included publications used the National Birth Defects Prevention Study,^{5,6} which was established in 1997 and includes population-based birth defects surveillance systems in 10 sites. Eight of 10 surveillance sites include live births, fetal deaths, and elective pregnancy terminations, thus mitigating, but not entirely eliminating, the risk of selection bias.⁵ Women were asked to recall use of multivitamins or supplements from 3 months before pregnancy through the last month of pregnancy, resulting in a maximum recall period of 3 years. Both publications are consistent in demonstrating a lack of association of folic acid supplementation with benefits (adjusted OR for anencephaly and spina bifida, 0.93 [95% CI, 0.82-1.06]⁵; adjusted OR for anencephaly, 1.2 [95% CI, 0.8-1.9]^{5,6}).

Three included studies were based on data from the Slone Birth Defects Study and were published in 1993,²² 2001,¹⁶ and 2011.⁷ The Slone Birth Defects Study began in 1976. It identified cases, largely from hospital discharge records; randomly selected controls; and identified exposure to folic acid supplements through an interview conducted within 6 months of delivery going back to 6 months before pregnancy. Over the course of several decades, the list of included sites and sources changed. The definition of exposure varied by publication, and the period of recall ranged from 15 to 17 months. The 1993 and 2001 publications relied on data from the era before food fortification and consistently demonstrated that daily use of supplements was associated with a lower risk of NTDs compared with nonuse (adjusted OR of 0.7 [level of precision here and below as reported by authors] [95% CI, 0.5-0.8] in the 2001 study¹⁶; adjusted OR of 0.6 [95% CI, 0.4-0.8] in the 1993 study²²). The 2011 Slone Birth Defects Study found no association of folic acid supplementation with the risk of spina bifida, regardless of the level of supplementation.⁷

Two other studies were conducted in the era before food fortification. Both studies drew on data from the California Birth Defects Monitoring program, using cases from 1985 to 1987¹⁷ and 1989 to 1991.²⁰ One study additionally drew on data from Illinois (also from 1985 to 1987, the NICHD Neural Tube Defects Study).¹⁷ Recall periods ranged from 13 to 17 months. The NICHD Neural Tube Defects Study reported no association of supplements with NTDs (OR, 1.00 [95% CI, 0.73-1.40]; $P = .97$).¹⁷ The study of California-only data found an OR of 0.65 (95% CI, 0.45-0.94) for any use in the 3 months before conception.²⁰

One case-control study from a limited data source collected data from January 1995 to February 1999 from 148 Mexican American women living along the Texas-Mexico border with NTD-affected pregnancies and 158 control women with normal live births.²¹ The average period of recall for this study was 13 months. The study, spanning the eras before and after food fortification, found a nonsignificant protective OR for NTDs (0.77 [95% CI, 0.19-3.22]) in the subset of women taking multivitamins containing folic acid daily for 3 months or less prior to conception; when adjusted for maternal age, education, obesity, and previous stillbirth or miscarriage, the direction of effect altered (adjusted OR, 1.12 [95% CI, 0.22-5.78; P value not reported).

Key Question 1b. Does the effect of folic acid supplementation on NTDs (first occurrence) differ by race or ethnicity?

Three case-control studies provide limited information about the effects of folic acid supplementation by racial and ethnic char-

acteristics (eTable 6 in the Supplement).^{6,7,20} The Slone Birth Defects Study (1998 to 2008) found no positive association with periconceptional folic acid supplementation for white women and a possible increased risk of spina bifida among consistent supplement users of Hispanic ethnicity when compared with nonusers⁷; however, the authors note that this finding may be attributable to chance.

The National Birth Defects Prevention Study (1998 to 2003) found that periconceptional supplement use was not associated with a lower risk of having a pregnancy affected by an NTD, and there were no differences in the effects of folic acid supplementation by race or ethnicity.⁶ The California Birth Defects Monitoring Program Study found that women who used any folic acid-containing vitamin in the 3 months before conception had a lower risk of having an NTD-affected pregnancy.²⁰ Reduction in risk for Hispanics was of smaller magnitude than that observed for non-Hispanic whites and blacks, but these results were not statistically significant and could have occurred because of chance.

Key Question 1c. Do the benefits of folic acid supplementation differ by dosage, timing, or duration of therapy?

One cohort study^{18,19} and 6 case-control studies^{6,7,17,20-22} provided information on the effects of dosage (eTable 7 in the Supplement) and timing (eTable 8 in the Supplement) of folic acid supplementation on NTDs. Four studies (1 cohort study¹⁹ and 3 case-control studies^{17,20,22}) reported on dose of folic acid supplementation. Five studies (1 cohort study¹⁸ and 4 case-control studies^{6,7,20,21}) reported on timing of folic acid supplementation. All included studies on dose predate the food-fortification era^{17,19,20,22} and generally failed to find a dose-response effect. An exception was the Slone Birth Defects Study (1988 to 1991),²² which suggested lower odds of NTDs with daily use vs less than daily use (OR, 0.57 [95% CI, 0.35-0.93]). Older studies on timing consistently show no effect, whereas newer studies varied, with 1 study (postfortification)⁶ showing a protective association with use before pregnancy on anencephaly but not spina bifida and the other not finding a protective association for spina bifida.⁷

Harms of Folic Acid Supplementation

Key Question 2a. Are there harms associated with folic acid supplementation to the mother, fetus, neonate, or child?

One RCT¹¹ and 1 cohort study³¹ provided information on twinning (Table 3). In a Hungarian trial comparing folic acid supplementation with a multivitamin to trace elements among informative pregnancies (defined as live births and stillbirths [late fetal deaths]), the proportion of twin pregnancies and twin births was not statistically significantly different between the 2 groups. Of the total pregnancies in the multivitamin group, 1.9% (46/2421) were determined to be twin gestations, compared with 1.4% (32/2346) of pregnancies in the trace element group (OR, 1.40 [95% CI, 0.89-2.21]; 54 more cases per 10 000 [95% CI, 18 fewer to 125 more]). The proportion of twin births (as opposed to pregnancies) was higher in the multivitamin group (93/2468 [3.8%]) than in the trace element group (64/2378 [2.7%]; OR, 1.41 [95% CI, 1.03-1.96]; 108 more cases per 10 000 [95% CI, 8 more to 207 more]). In a subgroup analysis of women receiving fertility drugs, the trial found no difference in twinning between the 2 groups.¹¹ A prospective cohort study found an increased odds (baseline adjustment for maternal age and parity) of twinning among pregnancies with folate use compared with those

Table 3. Results of Studies Examining Harms of Folic Acid Supplementation (Key Question 2)^{a,b}

| Source | Design | Period of Exposure | Population | Definition of Exposure | Timing of Measurement of Exposure | Outcome | | Exposed | | Not Exposed | | Measure (95% CI) |
|------------------------------------|---------------|--------------------|--|---|---|---|--|---|--|---|---|----------------------|
| | | | | | | With Outcome | Total | With Outcome | Total | With Outcome | Total | |
| Czeizel et al. ^{11, 1994} | RCT | 1984-1992 | Women planning a pregnancy without any delayed conception or infertility and not currently pregnant, Hungary | Assigned to daily use of multivitamins containing folic acid for 28 d before conception and at least until the date of the second missed menstrual period | Prospective | Multiple pregnancies for all pregnancies | Multiple pregnancy cases in exposed group: 46 | Informative pregnancies in exposed group: 2421 ^c | Multiple pregnancy cases in control group: 32 | Informative pregnancies ending in live births or stillbirths in control group: 2346 | Informative pregnancies (all ending in live births or stillbirths) in control group: 2346 | OR, 1.40 (0.89-2.21) |
| Vollset et al. ^{31, 2005} | Cohort | 1998-2001 | Women with singleton and twin pregnancies, Norway | Preconceptional use of folic acid | Retrospective, from birth notification forms and supplemented with forms filled in by mothers at 18-20 wk gestation | Multiple pregnancies among women receiving clofibrate | Multiple pregnancy cases in exposed group: 19 | Informative pregnancies in exposed group: 141 | Multiple pregnancy cases in control group: 12 | Informative pregnancies ending in live births or stillbirths in control group: 143 | Multiple pregnancy cases in control group: 12 | OR, 1.70 (0.79-3.65) |
| Vollset et al. ^{31, 2005} | Cohort | 1998-2001 | Women with and twin pregnancies, Norway | Preconceptional use of folic acid | Retrospective, from birth notification forms and supplemented with forms filled in by mothers at 18-20 wk gestation | Twin pregnancies with adjustments for maternal age and parity | Multiple pregnancy cases in exposed group for all women: 329 | Exposed group: 11 077 | Multiple pregnancy cases in comparison group: 2825 | Comparison group: 164 965 | Multiple pregnancy cases in comparison group: 2825 | OR, 1.59 (1.41-1.78) |
| Crider et al. ^{26, 2013} | Meta-analysis | 1998-2007 | Women with and without use of folic acid supplementation during pregnancy, Australia, the Netherlands, Norway, United States, United Kingdom | Periconceptional or first trimester | Retrospective (with respect to exposure), exposure data collected during pregnancy | Asthma | NR | NR | NR | NR | NR | RR, 1.01 (0.78-1.30) |
| Crider et al. ^{26, 2013} | Meta-analysis | 1998-2007 | Women with and without use of folic acid supplementation during pregnancy, Australia, the Netherlands, Norway, United States, United Kingdom | Periconceptional or first trimester | Retrospective (with respect to exposure), exposure data collected during pregnancy | Wheezing in infants/toddlers; asthma in children | NR | NR | NR | NR | NR | RR, 1.05 (1.02-1.09) |
| Yang et al. ^{34, 2015} | Meta-analysis | NR | Women with and without use of folic acid supplementation during pregnancy, Australia, the Netherlands, United States, United Kingdom | Periconceptional period through pregnancy | Retrospective (with respect to exposure), exposure data collected during pregnancy | Child asthma | NR | NR | NR | NR | NR | OR, 1.06 (0.99-1.14) |

Abbreviations: IVF, in vitro fertilization; LRTI, lower respiratory tract infection; NR, not reported; OR, odds ratio; RR, relative risk; URTI, upper respiratory tract infection; USPSTF, US Preventive Services Task Force.

^a All studies were rated as fair quality with the exception of Crider et al, 2013²⁶ (which was rated good quality), based on criteria developed by the USPSTF.² Cochrane methodologists^{37,38} and other international groups.⁴⁰

^b A third meta-analysis,³⁵ consisting of a subset of the primary studies in other 2 meta-analyses described above^{26,34,35} and is therefore not described in this table.

with no folate supplementation.³¹ With further adjustment for in vitro fertilization, the odds were attenuated and no longer statistically significant (1.04 [95% CI, 0.91-1.18]).

Eight articles^{25,27-30,32,33,36} synthesized in 3 systematic reviews^{26,34,35} reported on respiratory harms (childhood asthma or wheezing and allergen-related outcomes). All included primary studies were observational, with attendant risks of misclassification and recall bias. The pooled estimate from 1 meta-analysis²⁶ focusing on the prepregnancy period through the first trimester (N not reported) found no evidence from 3 studies^{29,30,32} of an association between maternal folic acid supplementation compared with no use and childhood asthma, with a pooled relative risk of 1.01 (95% CI, 0.78-1.30; $P = .95$; $I^2 = 0.00$; $P = .73$).²⁶ A second meta-analysis (n = 14 438)³⁴ included 5 studies^{25,29,30,32,33} and found no association between folic acid supplementation during the periconceptional period or pregnancy and the development of childhood asthma (OR, 1.06 [95% CI, 0.99-1.14]) but reported wide variations in the dose of folic acid supplementation across included studies. A third meta-analysis,³⁵ consisting of a subset of the primary studies in other meta-analyses, also reported no statistically significant association of folic acid supplementation with asthma, wheezing, atopic dermatitis, eczema, and sensitization.

One trial¹³ also reported on potential adverse effects of folic acid supplementation, many of which are common pregnancy symptoms, such as weight gain, gastrointestinal symptoms, and rashes. The study found no statistically significant differences in the reporting of most of these symptoms between the 2 groups from before pregnancy through pregnancy confirmation.

Key Question 2b. Do the harms of folic acid supplementation differ by dosage, timing, or duration of therapy?

One study separated the study population into tertiles of folate taken as vitamin supplements (<0.2 mg/d, 0.2 to 0.499 mg/d, and ≥ 0.5 mg/d) and compared the second and third tertiles to the first for the incidence of any allergic disease, sensitization, recurrent wheezing, eczema, food reactions, IgE-mediated food allergy, and sensitization to food allergens (eTable 9 in the [Supplement](#)). All results had wide confidence intervals spanning or overlapping the line of no difference.³⁶

Two of the cohort studies included in a previously published meta-analysis²⁶ examined the association between prenatal use of a supplement containing folic acid (compared with no use) in the second or third trimester and asthma or wheezing in childhood (eTable 10 in the [Supplement](#)).^{25,27} Of the 15 associations evaluated across 2 studies, only 1 association was significantly increased (adjusted prevalence ratio for maternal report of wheezing at 1 year, 1.20 [95% CI, 1.04-1.39]).²⁵ Three cohort studies examined the use of supplements containing folic acid during the second or third trimester and risk of other allergic outcomes.^{25,27,33} The meta-analysis reported no significant findings in 38 reported associations across these 3 studies.²⁶

A meta-analysis examined the incidence of asthma and wheezing by timing of supplementation (prepregnancy, early pregnancy, other period in pregnancy).³⁵ Four of 5 reported associations showed no statistically significant association of folic acid supplementation with asthma or wheezing in childhood. The 1 statistically significant association with wheezing in childhood was associated with exposure in early pregnancy (relative risk, 1.06 [95% CI, 1.02-1.09]).²⁷⁻²⁹

Discussion

A summary of findings in this evidence review is found in [Table 4](#) and [Table 5](#). Most of the studies included in this review have broad eligibility criteria; their participants are representative of the US primary care population. Early studies (1 trial, cohort and case-control studies) provided consistent evidence of benefit. After the publication of the Hungarian trial and other trials in women with recurrent NTDs (not included in this review), the evidence of benefit pointed to the need for large-scale public health interventions; the United States initiated the addition of folate to grain products in 1998.⁴¹ The evidence of benefit also made the conduct of additional trials unethical. As a consequence, all subsequent studies relied on observational data using case-control designs. These case-control studies do not show a protective association.

There was no consistent evidence of variation in benefits for subpopulations or by dose or timing. There was also no consistent evidence of an increased risk of twinning or childhood respiratory illnesses or variation in these outcomes by timing or dose.

Although the effect of food fortification may explain lack of benefit in more recent studies, study design flaws and inadequate sample size in these studies are also important considerations. All included observational studies in this review contain inherent and unavoidable sources of bias. Prospective cohort studies may not be able to ascertain all NTD cases. Retrospective studies have a risk of recall bias. In the case-control studies included in this review, women were asked to recall frequency and dose of supplements over a relatively short period of exposure (around the time of conception) occurring between 13 months and 3 years prior to the interview. Both of the risks of bias described above (case ascertainment and recall) will reduce the differences between study groups. The relative rarity of the outcome and the difficulty of adequately powering studies also complicates the interpretation of the results.

An additional consideration in weighing the relative contributions of folic acid supplementation and food fortification is the extent of benefit provided by food fortification. Estimates of folate sufficiency of intake vary widely by measure. When the highest threshold, the recommended usual intake of 0.4 mg/d, is used, National Health and Nutrition Examination Survey data from 2003 to 2006 suggest that 76% of nonpregnant women aged 15 to 44 years did not consume the recommended daily intake. Among all women, the median intake of folate overall was 0.245 mg/d.⁴² The proportion of women not consuming the recommended usual intake varies from 70 to 91% by race and ethnicity.

Rather than using a daily 400- μ g dosage to define adequate intake, another approach is to set the threshold for insufficiency based on red blood cell folate concentrations. A threshold of 400 ng/mL (906 nmol/L) or more is based on an association of the threshold with an NTD prevalence of more than 9 per 10 000 live births. This threshold yields an estimate suggesting a lower level of insufficiency, on average, with 22.8% of nonpregnant women aged 12 to 49 years having suboptimal red blood cell folate concentrations for NTD prevention.⁴³ Levels vary by use of dietary supplements containing folic acid, consumption of man-

Table 4. Summary of Evidence for Benefits of Folic Acid Supplementation (Key Question 1)

| No. of Studies (Study Designs), No. of Participants | Summary of Findings | Consistency/Precision | Reporting Bias | Overall Quality | Body of Evidence Limitations | Assessment of Strength of Evidence for Key Question | Applicability |
|--|--|---|----------------|-----------------|---|--|--------------------------------------|
| Key Question 1a: Extent to Which Folic Acid Supplementation Reduces the Risk for NTDs | | | | | | | |
| 12 (1 RCT, ^{8,13,15} 2 cohort studies, ^{14,18,19} 8 case-control studies, ^{5-7,16,17,20-22} 1 systematic review ^{23,24}); N > 41 802 | RCT (prefortification): Peto OR for NTDs; 0.13 (95% CI, 0.03-0.65; P = .01) ^{8,13,15} Cohort studies (prefortification): adjusted OR for NTDs, 0.11 (95% CI, 0.01-0.91) ¹⁴ , OR for NTDs, 0.27 (95% CI, 0.11-0.63) ^{18,19} Case-control studies (prefortification): results include: adjusted OR for NTDs, 0.7 (95% CI, 0.5-0.8) ¹⁶ ; adjusted OR for NTDs, 0.6 (95% CI, 0.4-0.8) ²¹ ; OR for NTDs, 0.65 (95% CI, 0.45-0.94) ²⁰ ; OR for NTDs, 1.00 (95% CI, 0.73-1.43) ¹⁷ Case-control studies (spanning prefortification and postfortification): adjusted OR for NTDs, 1.12 (95% CI, 0.22-5.78) ²¹ Case-control studies (postfortification): OR for NTDs, 1.11 (95% CI, 0.74-1.65) for consistent users ⁷ ; adjusted OR for NTDs (anencephaly + spina bifida), 0.93 (95% CI, 0.82-1.06) ⁵ ; adjusted OR for anencephaly, 1.2 (95% CI, 0.8-1.9) ⁶ ; adjusted OR for spina bifida: 1.4 (95% CI, 1.0-1.8) ⁶ | Consistency: generally consistent within the prefortification and postfortification eras, inconsistent over time Precision: wide CIs but clear indication of benefit in the prefortification era, narrower CIs with CIs spanning the null in postfortification era | Undetected | Fair | No new trials can be conducted on this topic. New studies must rely on observational data with inherent risks of case ascertainment bias or recall bias (retrospective studies) | High for prefortification data; low for postfortification data | Generally applicable to primary care |
| Key Question 1b: Differences in Effect of Folic Acid Supplementation on NTDs by Race/Ethnicity | | | | | | | |
| 3 (3 case-control studies ^{6,7,20}); N = 11 154 | No effect in one study ⁶ ; higher risk in second (adjusted OR for NTDs for Hispanic women, 2.20 (95% CI, 0.98-4.92) ⁷ ; less protective effect in third ²⁰ ; risk reduction less marked for Hispanic women (OR for NTDs, 0.96 (95% CI, 0.44-2.10) than non-Hispanic whites (OR for NTDs, 0.62 (95% CI, 0.35-1.10) or blacks (OR for NTDs, 0.54 (95% CI, 0.09-3.20) | Inconsistent Imprecise | Undetected | Fair | Small numbers in each comparison, effects possibly due to chance | Low | Generally applicable to primary care |
| Key Question 1c: Differences in Effect of Folic Acid Supplementation on NTDs by Dosage, Duration, and Timing | | | | | | | |
| Dosage: 4 (1 cohort study, ^{18,19} 3 case-control studies ^{17,20,22}); n = 26 791 Duration: 0 Timing: 5 (1 cohort study, ^{18,19} 4 case-control studies ^{6,7,20,21}); N = 26 808 | No indication of dose response in 3 of 4 studies. One study shows lower odds for daily use vs less than daily use (OR for NTDs, 0.57 (95% CI, 0.35-0.93) ²² Duration: none Timing: Calculated OR for NTDs from cohort study for use wk 1-6 vs wk 7 and later, 0.29 (95% CI, 0.14-0.60) ^{18,19} Older case-control studies consistently show no effect of timing, ^{20,21} 1 new study (postfortification) shows a protective effect of use before pregnancy on anencephaly but not spina bifida. ⁶ The other new study did not find a protective effect for spina bifida. ⁷ | Inconsistent Imprecise | Undetected | Fair | Small numbers in each comparison, effects possibly due to chance, studies use different measures of dose and timing | Low | Generally applicable to primary care |

Abbreviations: NTD, neural tube defect; OR, odds ratio; RCT, randomized clinical trial.

Table 5. Summary of Evidence for Benefits or Harms of Folic Acid Supplementation (Key Question 2)

| No. of Studies (Study Designs) | Summary of Findings | Consistency/Precision | Reporting Bias | Overall Quality | Body of Evidence Limitations | Assessment of Strength of Evidence for Key Question | Applicability |
|--|---|--|----------------|-----------------|---|---|--------------------------------------|
| Key Question 2a: Harms Associated With Folic Acid Supplementation | | | | | | | |
| Twining in women: 2 (1 trial, ¹¹ 1 cohort ³¹); N = 7387 | The trial found no statistically significant differences in twin pregnancy rate (OR for twin pregnancy, 1.40 [95% CI, 0.89-2.21]). ¹¹ The cohort study ³¹ found that the higher risk of twin birth for folic acid supplementation use (OR for twin birth, 1.59 [95% CI, 1.41-1.78]) was attenuated once potential misclassification was accounted for (1.04 [95% CI, 0.91-1.18]). ³¹ | Consistent Imprecise | Undetected | Fair | Low event rate, wide CIs | Moderate for no effect | Generally applicable to primary care |
| Childhood asthma, wheezing, allergy: 11 (3 systematic reviews, ^{26,34,35} 8 observational studies ^{25,27-30,32,33,36}); N > 14 438 | No effect for a large majority of comparisons and outcomes ^{25-30,32-36} | Consistent Precise | Undetected | | Variable measures of outcomes and exposure, all observation studies with risks of bias from case ascertainment and recall | Moderate for no effect | Generally applicable to primary care |
| Other adverse events in women: 1 (1 RCT ¹³); N = 4862) | Increased risk for weight gain, diarrhea, constipation; reduced risk for irregular defecation; no difference for increased appetite, lack of appetite, exanthema, heartburn, and vertigo ¹³ | Consistency unknown, single study, imprecise | Undetected | | Low event rate, wide CIs | Low for no effect | Generally applicable to primary care |
| Key Question 2b: Differences in Harms Associated With Folic Acid Supplementation by Dosage, Timing, and Duration | | | | | | | |
| Dosage: 2 (1 systematic review, ²⁶ 1 observational study ³⁶); N = 484 Duration: 0 Timing of asthma, wheezing, allergy: 5 (2 systematic reviews, ^{26,35} 3 observational studies ^{25,27,33}); No. varies by outcome | Dosage: no consistent increase in the risk of childhood asthma, wheezing, or allergies by dosage ^{26,36} Duration: none Timing: no consistent increase in the risk of childhood asthma, wheezing, or allergies by timing ^{25-27,33,35} | Consistent Precise | Undetected | | Variable measures of outcomes and exposure, all observation studies with risks of bias from case ascertainment and recall | Low for no effect | Generally applicable to primary care |

Abbreviations: NTD, neural tube defect; OR, odds ratio; RCT, randomized clinical trial.

datorily fortified enriched cereal grain products as the only source of folic acid, non-Hispanic black or Hispanic race and ethnicity, and current smoking status.

Very few women exceed the upper level for folic acid consumption (1000 µg/d). According to the 2015 Dietary Guideline Advisory Committee report, less than 3% of women aged 14 to 50 years were getting more than 1000 µg/d from food, bever-

ages, and dietary supplements, based on National Health and Nutrition Examination Study data collected from 2007-2010.⁴⁴

The limitations of this review arise from its scope and the limitations of the evidence. As with the previous USPSTF review on this topic,^{23,24} interventions were restricted to folic acid supplementation and did not evaluate the effectiveness of food fortification, counseling to increase dietary intake, or screening for NTDs. The review

did not examine the effects of folic acid supplementation on benefits other than averted NTDs. In addition, it did not evaluate systematically the effect of folic acid supplementation among high-risk populations such as women with previous pregnancies with NTDs.

Limitations of the evidence relate to insufficient data and the quality of evidence as a whole. There was very limited information on differences in benefits and risks of folic acid supplementation by race, ethnicity, dose, and timing and no information on duration. Regarding the overall quality of evidence, ethical considerations limit the conduct of RCTs for this question.

Conclusions

In studies conducted before the initiation of food fortification in the United States in 1998, folic acid supplementation provided protection against neural tube defects. Newer postfortification studies have not demonstrated a protective association but have the potential for misclassification and recall bias, which can attenuate the measured association of folic acid supplementation with neural tube defects.

ARTICLE INFORMATION

Author Contributions: Dr Viswanathan had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Viswanathan, Treiman, Nicholson.

Acquisition, analysis, or interpretation of data: Viswanathan, Treiman, Middleton, Coker-Schwimmer, Nicholson.

Drafting of the manuscript: Viswanathan, Treiman, Middleton, Nicholson.

Critical revision of the manuscript for important intellectual content: Viswanathan, Coker-Schwimmer, Nicholson.

Statistical analysis: Viswanathan, Nicholson.

Obtained funding: Viswanathan.

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Supervision: Viswanathan.

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