JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Folic Acid Supplementation to Prevent Neural Tube Defects
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 birth defects in the US.

OBJECTIVE To review new evidence on the benefits and harms of folic acid supplementation for the prevention of neural tube defects to inform the US Preventive Services Task Force.

EVIDENCE REVIEW Sources included PubMed, Cochrane Library, Embase, and trial registries from July 1, 2015, through July 2, 2021; references; and experts, with surveillance through February 10, 2023. Two investigators independently reviewed English-language randomized studies and nonrandomized cohort studies in very highly developed countries that focused on the use of folic acid supplementation for the prevention of neural tube defect–affected pregnancies; methodological quality was dually and independently assessed.

FINDINGS Twelve observational studies (reported in 13 publications) were eligible for this limited update (N = 1 244 072). Of these, 3 studies (n = 990 372) reported on the effect of folic acid supplementation on neural tube defects. For harms, 9 studies were eligible: 1 randomized clinical trial (n = 431) reported on variations in twin delivery, 7 observational studies (n = 761 125) reported on the incidence of autism spectrum disorder, and 1 observational study (n = 429 004) reported on maternal cancer. Two cohort studies and 1 case-control study newly identified in this update reported on the association between folic acid supplementation and neural tube defects (n = 990 372). One cohort study reported a statistically significant reduced risk of neural tube defects associated with folic acid supplementation taken before pregnancy (adjusted relative risk [aRR], 0.54 [95% CI, 0.31-0.91]), during pregnancy (aRR, 0.62 [95% CI, 0.39-0.97]), and before and during pregnancy (aRR, 0.49 [95% CI, 0.29-0.83]), but this association occurred for only the later of 2 periods studied (2006-2013 and not 1999-2005). No other statistically significant benefits were reported overall. No study reported statistically significant harms (multiple gestation, autism, and maternal cancer) associated with pregnancy-related folic acid exposure.

CONCLUSIONS AND RELEVANCE New evidence from observational studies provided additional evidence of the benefit of folic acid supplementation for preventing neural tube defects and no evidence of harms related to multiple gestation, autism, or maternal cancer. The new evidence was consistent with previously reviewed evidence on benefits and harms.

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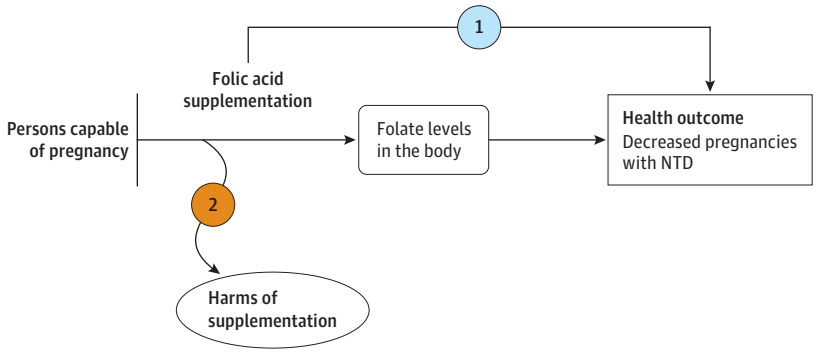
Neural tube defects are major congenital malformations often caused by low folate concentrations in the body at the time of conception. These defects frequently result in significant disability or death for affected fetuses and children. Strategies that enhance folic acid uptake before pregnancy offer the best chance of prevention.

In 2017, the US Preventive Services Task Force (USPSTF) concluded that folic acid supplementation in the periconceptional period has substantial benefits in reducing the risk of neural tube defects in the developing fetus[1] and reaffirmed its 2009 recommendation that all persons who are planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400-800 µg) of folic acid (A recommendation). The 2017 USPSTF recommendation was based on previously reviewed evidence from a randomized clinical trial and observational studies reporting reduced neural tube defects with supplementation and no consistent evidence of harms such as multiple gestation, maternal adverse effects, or child respiratory illness.

This limited evidence update aimed to identify studies published since the previous (2017) evidence review[2] conducted for the USPSTF to inform a reaffirmation of the current recommendation.

Figure. Analytic Framework: Folic Acid Supplementation to Prevent Neural Tube Defects



Key questions

1 a. To what extent does folic acid supplementation reduce the risk for NTDs (first occurrence) in persons capable of getting pregnant?

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

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

2 a. Are harms associated with folic acid supplementation to the pregnant person, fetus, neonate, or child?

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

Evidence reviews for the US Preventive Services Task Force (USPSTF) use an analytic framework to visually display the key questions that the review will address to allow the USPSTF to evaluate the effectiveness and safety of a preventive service. The questions are depicted by linkages that relate to interventions and outcomes. Further details are available from the USPSTF procedure manual.[3] NTD indicates neural tube defect.

Methods

An analytic framework and 2 key questions guided the limited evidence update (**Figure**). A literature search of PubMed/MEDLINE, the Cochrane Library, Embase, and trial registries was conducted from July 1, 2015, through July 2, 2021. Additional sources included reference lists of retrieved articles, outside experts, and public commenters, with ongoing surveillance of the literature through February 10, 2023. Two investigators independently evaluated the eligibility of all abstracts and articles and rated study quality using predefined criteria.[4] Detailed methods and results are available in the full evidence report.[4]

English-language randomized and nonrandomized studies that focused on the use of folic acid supplementation (by itself or in multivitamins) for the prevention of neural tube defect–affected pregnancies in persons capable of getting pregnant were eligible. Studies conducted in very highly developed countries and that investigated potential harms of folic acid supplementation, such as maternal cancer and autism spectrum disorder, were also eligible. Ineligible studies included poor-quality studies and those focusing solely on persons taking antiseizure medications or with a history of neural tube defects in previous pregnancies.

Results

Twelve observational studies (reported in 13 publications[5-17]) (**Table**) were eligible for this limited update (N = 1 244 072 [from nonoverlapping cohorts]). Of these, 3 studies (n = 990 372) assessed the effect of folic acid supplementation on neural tube defects.[5-8] No studies examined differences by race or ethnicity. For harms, 9 studies were eligible; 1 randomized clinical trial (n = 431) assessed variations in twin delivery,[9] 7 observational studies (n = 761 125) examined the incidence of autism spectrum disorders,[10-16] and 1 observational study (n = 429 004) reported on maternal cancer.[17] The Table also reports details on studies from the 2017 evidence review.[18-47]

Benefits of Folic Acid Supplementation

Regarding the benefits of folic acid supplementation, 2 cohort studies and 1 case-control study in this update examined the association between folic acid supplementation and neural tube defects (n = 990 372).[5-8] Food fortification and supplementation practices varied by setting. Of these studies, 1 cohort study set in Norway (no mandatory fortification) reported on neural tube defects among live births and stillborn infants from 1999 to 2013 overall and also stratified results into 2 separate periods: 1999 to 2005 and 2006 to 2013.[6] The authors performed this stratified analysis because they found that the overall adjusted relative risk (aRR) was affected by year of birth. Several external events of importance were cited to explain differences by period: the introduction of folic acid recommendations in 1999, inclusion of 0.2 mg of folic acid in multivitamin supplements from 2004 onward (before 2004, most multivitamins did not include folic acid), and increased adherence to folic acid recommendations in the second half of the period analyzed (2006-2013).[6] The authors reported no statistically significant benefits in the first of the 2 periods (1999-2005), regardless of timing of supplementation (before pregnancy, during pregnancy, or before and during pregnancy). In contrast, in the second period (2006-2013), the authors reported a statistically significant reduced risk of neural tube defects associated with folic acid supplementation taken before pregnancy (aRR, 0.54 [95% CI, 0.31-0.91]), during

Table. Summary of Evidence From Limited Update Review: Folic Acid Supplementation to Prevent Neural Tube Defects

Key question	Evidence summary in 2017[2]	Summary of new evidence	Limitations of new evidence	Consistency of new evidence with prior evidence findings
KQ1: Benefits of folic acid supplementation				
1a: Effects of folic acid supplements on risk of NTDs	12 Studies (1 RCT, 2 cohort, 8 case-control, 1 previous review); n > 41 802 Generally consistent evidence within the prefortification (indicating benefit) and postfortification (no statistically significant differences) eras; inconsistent over time 1 RCT (prefortification): Peto OR for NTD, 0.131 (95% CI, 0.026-0.648); *P* = .01[29,42-47] 2 Cohort studies (prefortification): aOR for NTD, 0.11 (95% CI, 0.01-0.91)[18] OR, 0.27 (95% CI, 0.11-0.63)[19,20] 4 Case-control studies (prefortification): aOR for NTD, 0.7 (95% CI, 0.5-0.8)[21] RR for NTD, 0.6 (95% CI, 0.4-0.8)[22] OR for NTD, 0.65 (95% CI, 0.45-0.94)[23] OR for NTD, 1.00 (95% CI, 0.73-1.40); *P* = .97[24] 1 Case-control study (spanning prefortification and postfortification eras): aOR for NTD, 1.12 (95% CI, 0.22-5.78)[25] 3 Case-control studies (postfortification): OR for NTD, 1.11 (95% CI, 0.74-1.65) for consistent users[26] aOR for NTD (anencephaly + spina bifida), 0.93 (95% CI, 0.82-1.06)[27] aOR (anencephaly), 1.2 (95% CI, 0.8-1.9)[28] aOR (spina bifida), 1.4 (95% CI, 1.0-1.8)[28] No new trials can be conducted on this topic New studies must rely on observational data with inherent risks of case ascertainment bias (in prospective cohort studies) or exposure recall bias (in retrospective studies)	3 Studies (2 cohort [3 publications[5-7]], 1 case-control[8]); N = 990 372 Norwegian cohort (no mandatory fortification) study reported no statistically significant associations in overall analysis (1999-2013) or the first period (1999-2005) with low adherence to folic acid supplementation recommendations Statistically significant associations from 2006-2013 with higher adherence to folic acid recommendations: Before pregnancy only (aRR, 0.54 [95% CI, 0.31-0.91])[6] During pregnancy only (aRR, 0.62 [95% CI, 0.39-0.97])[7] Before and during pregnancy (aRR, 0.49 [95% CI, 0.29-0.83])[7] No consistently and statistically significant associations in Japanese cohort of general population (no mandatory fortification) (aOR, 0.62 [95% CI, 0.23-1.71] for preconceptional use when compared with use after pregnancy recognition or no use)[5] or US and Canadian case-control study (postfortification study) of participants with prepregnancy diabetes or pregestational obesity for exposures measured as less than daily, daily, <0.4 mg, 0.4 mg to <1.0 mg[8]	Heterogenous populations with different levels of food fortification and diet patterns; methodological limitations in foundational evidence also apply	New studies have some evidence of benefit for reducing NTDs and do not change conclusions from foundational evidence
1b: Differences in effect of folic acid supplements on NTDs by race or ethnicity	3 Case-control studies; n = 11 154 Inconsistent and imprecise findings from fair-quality studies suggesting no differences: No effect in first study[28] Higher risk in second study (aOR for Hispanic women with consistent use compared with nonuse, 2.20 [95% CI, 0.98-4.92])[26] Less protective effect in third study (OR, 0.96 [95% CI, 0.44-2.10] for Hispanic women vs 0.62 [95% CI, 0.35-1.10] for non-Hispanic White women vs 0.54 [95% CI, 0.09-3.20] for Black women)[23] Small numbers in each comparison, differences in direction of estimate of effects possibly due to chance	No new evidence	NA	NA

(continued)

Table. Summary of Evidence From Limited Update Review: Folic Acid Supplementation to Prevent Neural Tube Defects (continued)

Key question	Evidence summary in 2017[2]	Summary of new evidence	Limitations of new evidence	Consistency of new evidence with prior evidence findings
1c: Differences in effect of folic acid supplements on NTDs by dosage, duration, and timing	Dosage: 4 studies (1 cohort, 3 case-control); n = 26 791 No indication of dose response in 3 of 4 studies[19,20,22-24]; 1 study showed lower odds for daily use vs less than daily use (OR, 0.57 [95% CI, 0.35-0.93])[22] Duration: 0 studies Timing: 5 studies (1 cohort, 4 case-control); n = 26 808 Calculated OR from cohort study for use weeks 1-6 vs weeks 7 and later, 0.29 (95% CI, 0.14-0.60)[19,20] Older studies consistently showed no effect of timing[23,25]; 1 new study (postfortification) showed a protective effect of use before pregnancy vs initiation in the first month of pregnancy on anencephaly but not spina bifida[28]; the other new study did not find a protective effect for spina bifida for consistent periconceptional use vs initiation in the first month of pregnancy[26] Small numbers in each comparison, effects possibly due to chance, studies used different measures of dose and timing	Dosage: 1 case-control study of women with prepregnancy obesity; n = 1429 Statistically significantly reduced association between NTD risk and exposure of 0.4 mg to <1.0 mg of folic acid supplementation daily (aOR, 0.54 [95% CI, 0.29-0.95]) but not for exposures of <0.4 mg (aOR, 1.29 [95% CI, 0.40-3.37]) or <0.4 mg or ≥1.0 mg (aOR, 0.84 [95% CI, 0.38-1.68])[8]; differences did not persist in sensitivity analysis Duration: 0 studies Timing: 1 cohort study (2 publications[6,7]); n = 896 674 Consistent benefits regardless of timing in 1 of 3 periods examined (2006-2013) (aRR before pregnancy only, 0.54 [95% CI, 0.31-0.91][6]; during pregnancy only, 0.62 [95% CI, 0.39-0.97][7]; and before and during pregnancy, 0.49 [95% CI, 0.29-0.83][7]; consistently no statistically significant differences for the other periods [1999-2013, 1999-2005])	Small numbers in each comparison, effects possibly due to chance	New studies do not change conclusions regarding dosage or timing
KQ2: Harms of folic acid supplementation				
2a: Harms associated with folic acid supplements: multiple gestation (twinning)	2 Studies (1 trial, 1 cohort); n = 7387 Trial found no statistically significant differences in twin pregnancy rate (RR, 1.4 [95% CI, 0.87-2.26])[29] Cohort study found higher risk of twin birth for folate use (OR, 1.59 [95% CI, 1.41-1.78]) that was attenuated once potential misclassification was accounted for (OR, 1.04 [95% CI, 0.91-1.18])[30] Low event rate, wide CIs	No new evidence	NA	NA
2a: Harms associated with folic acid supplements: childhood asthma, allergy, wheezing	3 Systematic reviews, 8 observational studies; n > 14 438 No effect for a large majority of comparisons and outcomes[31-41] Variable measures of outcomes and exposure, all observation studies with risks of bias from case ascertainment and recall	No new evidence	NA	NA
2a: Harms associated with folic acid supplements: other adverse events in women	1 RCT; 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[42] Low event rate, wide CIs	No new evidence	NA	NA
2a: Harms associated with folic acid supplements: autism	No eligible evidence	7 Studies (6 fair-quality cohort[10-15] and 1 fair-quality case-control[16]); n = 761 125 Studies set in 4 countries (Israel, Sweden, Denmark, Norway); varied measures of exposure, comparators, and outcomes; generally no statistically significant associations; 3 publications on 2 populations in Israel[15] and Norway,[12,14] respectively, reported some benefits	No study reported harms, but differences in statistically significant associations (benefits vs no evidence of difference) may stem from differences in measurement of exposure, choice of comparator, and controls for confounding	NA

(continued)

Table. Summary of Evidence From Limited Update Review: Folic Acid Supplementation to Prevent Neural Tube Defects (continued)

Key question	Evidence summary in 2017[2]	Summary of new evidence	Limitations of new evidence	Consistency of new evidence with prior evidence findings
2a: Harms associated with folic acid supplements: maternal cancer	No eligible evidence	1 Cohort study;[17] n = 429 004 HR for 1 pregnancy with exposure to folic acid supplementation vs no exposure in pregnancy, 1.08 (95% CI, 1.00-1.18)[17] HR for ≥2 pregnancies with exposure to folic acid supplementation vs no exposure in pregnancy, 1.06 (95% CI, 0.91-1.22)[17]	Potential for unmeasured confounding and recall bias in the classification of the intervention	NA
2b: Differences in harms associated with folic acid supplements by dosage, timing, and duration: twinning	No eligible evidence	1 Trial[9]; n = 431 RR, 0.45 (95% CI, 0.11-1.77) for twin deliveries with exposure to 4-mg folic acid supplementation vs exposure to 0.4-mg folic acid supplementation; both groups exposed before conception and through 12 weeks of gestation	Applicability uncertain to unplanned pregnancies	NA
2b: Differences in harms associated with folic acid supplements by dosage, timing, and duration: childhood asthma, allergy, wheezing	Dosage: 1 systematic review, 1 observational study; n = 484 No consistent increase in the risk of childhood asthma, wheezing, or allergies by timing[32,41] Duration: 0 studies Timing: 2 systematic reviews, 3 observational studies; N varies by outcome No consistent increase in the risk of childhood asthma, wheezing, or allergies by timing[31,33,34,40,41] Variable measures of outcomes and exposure, all observational studies with risks of bias from case ascertainment and recall	No new evidence	NA	NA
2b: Differences in harms associated with folic acid supplements by dosage, timing, and duration: autism	No eligible evidence	Dosage: 3 studies (2 cohort,[11,12] 1 case-control)[16]; n = 194 281 Overlap in CIs with exposure to folic acid supplementation in different doses vs no or very low exposure to folic acid supplementation in pregnancy, all not statistically significant Duration: 0 studies Timing: 2 cohort studies,[11,12] n = 120 235 Overlap in CIs with exposure to folic acid supplementation in different time intervals vs no exposure to folic acid supplementation in pregnancy, all but 1 estimate not statistically significant; initiation in weeks 5 to 8 associated with benefit (14/16 184 vs 32/14 721; aOR, 044 [95% CI, 0.23-0.83])[12]	Potential for unmeasured confounding and recall bias in the classification of the intervention	NA

Abbreviations: aOR, adjusted odds ratio; aRR, adjusted relative risk; HR, hazard ratio; KQ, key question; NTD, neural tube defect; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk.

pregnancy (aRR, 0.62 [95% CI, 0.39-0.97]), and before and during pregnancy (aRR, 0.49 [95% CI, 0.29-0.83]).[6]

The second cohort study, set in Japan (no mandatory food fortification), reported no statistically significant differences associated with adequate (preconception) folic acid supplementation (adjusted odds ratio [aOR], 0.62 [95% CI, 0.23-1.71]) when compared with inadequate use (use after pregnancy recognition or no use).[5] The third study, a case-control study set in the US and Canada in the period following food fortification, reported on participants with pregestational diabetes and prepregnancy obesity.[8] The study reported that cases occurred more often among persons with unplanned pregnancies.[8] Authors reported a statistically significant reduction in neural tube defects in women with prepregnancy obesity taking 0.4 mg to 1 mg of folic acid, when compared with women taking no supplementation and adjusting for maternal age (aOR, 0.54 [95% CI, 0.29-0.95]).[8] Results adjusting for planned pregnancy rather than maternal age were similar but not statistically significant (aOR, 0.57 [95% CI, 0.30-1.02]).[8] Across all 3 studies, no other statistically significant benefits were reported overall or by dose (1 study[8]) or timing (1 study[6,7]).

Harms of Folic Acid Supplementation

No study of harms (multiple gestation, autism, and maternal cancer) reported significant associations with pregnancy-related folic acid exposure.[9-17]

Discussion

This evidence review identified 3 new observational studies reporting on the association between folic acid supplementation before or during pregnancy and neural tube defects in offspring. Mandatory food fortification and supplementation practices varied by geography and period of investigation and contributed to heterogeneity across studies. Nevertheless, these new studies provided additional evidence of the benefit of folic acid supplementation for preventing neural tube defects. Nine new observational studies found no evidence of harms related to multiple gestation, autism, or maternal cancer. This new evidence is consistent with previously reviewed evidence on the benefits and harms of folic acid supplementation to prevent neural tube defects.

ARTICLE INFORMATION

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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, Urrutia, Kahwati.
Acquisition, analysis, or interpretation of data: Viswanathan, Urrutia, Hudson, Middleton.
Drafting of the manuscript: Viswanathan, Urrutia, Hudson, Middleton.
Statistical analysis: Viswanathan.
Obtained funding: Viswanathan, Kahwati.
Administrative, technical, or material support: Viswanathan, Hudson, Middleton, Kahwati.
Supervision: Viswanathan.

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Role of the Funder/Sponsor: Investigators worked with USPSTF members and AHRQ staff to develop the scope, analytic framework, and key questions for this review. AHRQ had no role in study selection, quality assessment, or synthesis. AHRQ staff provided project oversight, reviewed the report to ensure the analysis met methodological standards, and distributed the draft for peer review. Otherwise, AHRQ had no role in the conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript findings. The opinions expressed in this document are those of the authors and do not represent the official position of AHRQ or the US Department of Health and Human Services.

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Editorial Disclaimer: This evidence report is presented as a document in support of the accompanying USPSTF recommendation statement. It did not undergo additional peer review after submission to *JAMA*.

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