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Folic Acid Supplementation: An Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Purpose: To assess the benefits and harms of folic acid supplementation in reproductive-age women for the prevention of neural tube defects.

Data Sources: Systematic review of studies from MEDLINE, the Cochrane Library, EMBASE unpublished literature, and trial registries through January 28, 2016; bibliographies from retrieved articles, outside experts, and reviewers.

Study Selection: Two investigators independently selected studies using a priori inclusion and exclusion criteria. We included studies that focused on the use of folic acid supplementation (by itself or in multivitamin or prenatal supplement form) for the prevention of neural tube defect (NTD)-affected pregnancies in women of childbearing age. We limited the evaluation of benefits to NTDs.

We excluded poor-quality studies and studies of prepubertal girls, men or women without the potential for childbearing, and NTD recurrence prevention; and studies in developing countries.

Data Extraction: One investigator extracted data and a second checked accuracy. Two reviewers independently rated the quality for all included studies, using predefined criteria.

Data Synthesis: We included 24 studies: 12 on the effect of folic acid supplementation NTDs, 3 on variation in the effect on NTDs by race/ethnicity, and 8 on variation by dosage or timing. For harms, we focused on two recent systematic reviews (SRs) on respiratory outcomes, which reported on several included studies. One SR also provided data on variation in harms by timing and dose. We paid particular attention in the analysis to variation in effect by study design and over time, particularly before and after food fortification in the United States (1998).

For the question of benefits of folic acid supplement on NTDs, we found a single randomized controlled trial (RCT), initiated in 1984 in Hungary, reporting a Peto odds ratio for NTDs of 0.131, 95% CI, 0.026 to 0.648, p=0.013. Two older cohort studies provided OR for NTDs of 0.11 (95% CI, 0.011 to 0.91) and 0.27 (95% CI, 0.12 to 0.59). Older case-control studies were also generally consistent with the evidence from the older RCT and cohort studies; odds ranged from 0.6 to 0.7. This evidence led to food fortification in the United States in 1998, after which no new trials or prospective cohort studies have been conducted. All newer evidence arises fromcase-control studies only. These newer studies, with inherently weaker designs, are consistent in not demonstrating a protective effect of folic acid supplements in NTDs, with odds ranging from 0.934 to 1.4, with confidence intervals spanning the null.

Regarding variations in benefits by race and ethnicity, we found three eligible studies. One found no effect by race/ethnicity, a second found a higher but nonsignificant risk of NTDs with folic acid supplementation among Hispanic women (adjusted OR for consistent users compared with nonusers, 2.20, 95% CI, 0.98 to 4.92, 2.20, 95% CI, 0.98 to 4.92), and a third found that the risk reduction was of smaller magnitude for Hispanic women when compared with white or black women. These inconsistent results could have occurred by chance. Regarding variation in

benefits, eight studies provided information. Of these, four studies provided information on dose, none on duration, and five on timing. We found no indication of a dose-response relationship in 3 of 4 studies. One study shows lower odds for daily use versus less than daily use (OR, 0.57; 95% CI, 0.35 to 0.93). Regarding timing, two older studies consistently showed no effect.

Two newer studies found no effect of timing for spina bifida, while one showed a protective effect with use before pregnancy for anencephaly.

Regarding harms, one trial and one cohort did not find evidence of statistically significant increased risk of twinning in women. The cohort study found that any increased risk of twinning was attenuated when the confounding effects of in vitro fertilization were accounted for. Two SRs evaluated childhood asthma, wheezing, or allergy and found no consistent evidence of harm. One trial evaluated the risks of adverse events in women and found a higher risk of folic acid supplementation for some events (weight gain, diarrhea, constipation) and not others (increased appetite, lack of appetite, exanthema, heartburn, and vertigo), but the event rate was very low and could have occurred by chance or as consequence of pregnancy. One SR did not find consistent evidence of an effect of folic acid supplementation on childhood asthma, wheezing, and allergy by timing or dose of intake.

Limitations: We restricted interventions to folic acid supplementation and did not include for interventions such as food fortification, counseling to increase dietary intake, or screening for NTDs. We found 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 use of RCTs to answer questions of efficacy. Observational studies carry limitations of case ascertainment and recall bias, and these two sources of bias can serve to reduce the observed effect of NTDs.

Conclusions: Studies conducted before food fortification in the United States in 1998, with fewer design flaws, show that folic acid supplementation provides protection against NTDs. Newer studies, conducted after food fortification with folic acid do not demonstrate this protective effect. These studies, however, have the potential for misclassification and recall bias, both of which can serve to attenuate the effect of folic acid supplementation on NTDs. Although mandatory food fortification in the United States has been accompanied by a decline in NTD prevalence, variations in intake continue to leave nearly a quarter of the U.S. population with suboptimal red blood cell folate concentrations, suggesting continued importance of folic acid supplement use.

Evidence of variations in effectiveness by race and ethnicity is inconsistent and could have occurred due to chance. We found no evidence of a dose-response effect, but studies had small numbers of cases for subanalyses. We did not find consistent evidence on timing of folic acid for benefits. We also did not find consistent evidence of harms, specifically twinning, respiratory outcomes, and other harms.

Table of Contents

Chapter 1. Introduction 1
Scope and Purpose 1
Prevalence and Burden of Illness 1
Etiology and Natural History 2
Risk Factors 2
Prevention 3
Rationale for Intervention 3
Intervention Strategies 3
Dietary Measures and Biomarkers of Folic Acid Intake 3
Sources of Folate and Folic Acid 4
Consumption of Folate and RBC Folate Concentration 5
Red Blood Cell Folate Concentration and Neural Tube Defects 5
Folic Acid Consumption and Pregnancy Intention 6
Promoting Folic Acid Consumption 6
Current Clinical Practice 7
Previous USPSTF Recommendation 7
Chapter 2. Methods 8
Key Questions and Analytic Framework 8
Search Strategies 8
Study Selection 9
Population 9
Interventions 9
Comparators 9
Outcomes and Timing 9
Settings 9
Study Designs 10
Data Abstraction and Quality Rating 10
Studies in the 2009 Report Meeting Inclusion Criteria 10
Data Synthesis and Analysis 10
Expert Review and Public Comment 10
USPSTF Involvement 11
Chapter 3. Results 12
Literature Search 12
Results 12
Key Question 1a: Effect of Folic Acid Supplementation on Neural Tube Defects in Women of Childbearing Age 12
Key Question 1b: Variation in Effect of Folic Acid Supplementation by Race and Ethnicity 19
Key Question 1c: Variation in Effect of Folic Acid Supplementation by Dosage, Timing, and Duration of Therapy 20
Key Question 2a: Harms of Folic Acid Supplementation in Women of Childbearing Age 21

Key Question 2b: Variation in Harms of Folic Acid Supplementation by Dose, Timing, and Duration of Therapy 24
Chapter 4. Discussion 26
Summary of Evidence 26
Evidence for Benefits of Folic Acid Supplementation 26
Evidence for Harms of Folic Acid Supplementation 27
Applicability of Evidence 28
Sufficiency of Intake 28
Variation of Intake From Diet and Other Sources 28
Differences by Age 29
Differences by Race and Ethnicity 29
Differences by Education 30
Differences by Income 30
Differences by Insurance Status 30
Differences by Employment Status 31
Differences by Marital Status 31
Differences by Pregnancy Intention 31
Differences by U.S. Versus Foreign Born and Years in the United States 31
Differences by Parity 31
Differences by Health Behaviors/Health Status 32
Effect of Folic Acid Supplementation Outside the Periconceptional Period on Neural Tube Defects 32
Variation in Effect of Folic Acid Supplementation by Medical Risk Factors 32
Diabetes 32
Maternal Obesity 33
Folic Acid Antagonists and Seizure Medications 34
Prior Neural Tube Defects 34
Other Fetal, Neonatal, or Maternal Benefits of Folic Acid Supplementation 35
Limitations of the Review 35
Future Research Needs 36
Conclusion 37
References 38

Figures

Figure 1. Analytic framework: Folic acid supplementation for the prevention of neural tube defects
Figure 2. Preferred reporting of systematic review and meta-analysis (PRISMA) tree
Figure 3. Folic acid supplementation and adverse events: Forest plot
Figure 4. Folic acid supplementation and neural tube defects by earliest year of recruitment: Forest plot
Figure 5. Folic acid supplementation and neural tube defects by study design: Forest plot

Tables

Table 1. Measures and Definitions
Table 2. Current guidelines for folic acid supplementation

Table 3. Study characteristics of studies on the effect of folic acid supplementation on neural tube defects
Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects
Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects
Table 6. Variations in the effect of folic acid supplementation neural tube defects by race and ethnicity
Table 7. Variations in effect of folic acid supplementation on neural tube defects by dosage
Table 8. Variations in effect of folic acid supplementation on neural tube defects by timing
Table 9. Harms of folic acid supplementation: Study characteristics of included twinning studies
Table 10. Harms of folic acid supplementation: Study characteristics of included asthma/wheezing studies
Table 11. Results of prospective studies on the associations between folic acid supplementation and twinning
Table 12. Results of meta-analyses on the associations between folic acid supplementation and asthma/respiratory illness
Table 13. Variation in harms of folic acid supplementation by timing
Table 14. Variation in harms of folic acid supplementation by dose
Table 15. Summary of evidence for folic acid supplementation
Table 16. Estimates of folate sufficiency

AppendiXes

Appendix A. Search Strategy and Detailed Methods
Appendix B. Inclusion/Exclusion Criteria
Appendix C. Excluded Studies
Appendix D. Risk of Bias Assessments for all Included Studies
Appendix E. Inclusion/Exclusion Status of Studies Included in 2009 Report
Appendix F. Overview of Study Characteristics
Appendix G. Ongoing Trials

Chapter 1. Introduction

Scope and Purpose

The U.S. Preventive Services Task Force (USPSTF or Task Force) will use this systematic review to update its 2009 recommendation on folic acid supplementation in women of childbearing age for the prevention of neural tube defects (NTDs) in their offspring. This report will summarize the evidence for the benefits and harms of folic acid supplementation and identify key gaps in the scientific literature. Evidence on folate fortification, counseling to increase dietary intake of folate (folic acid or food folate), or screening for NTDs is outside of the scope of this report.

Condition Background

Definition

NTDs are abnormalities that can occur in the brain, spine, or spinal canal of a developing embryo and are present at birth.[1] During an embryo's development, specific cells form a neural tube that later becomes the spinal cord, the brain, and the nearby structures (e.g., spinal column) that protect them. The top of the neural tube becomes the brain and the remainder becomes the spinal cord. When the neural tube does not close completely, a hole in the spinal column is left or another type of defect develops.[1] NTDs cover numerous conditions including spina bifida, encephaloceles and anencephaly. Spina bifida occurs when the neural tube in the cranial region or along the spine does not close by the 28th day of gestation.[2] Spina bifida can range from mild (no noticeable disability) to severe (limitations in physical movement and function, paralysis, cognitive deficits). Anencephaly is a more severe NTD that results in the fetus having little to no brain matter; the fetus could also lack part of its skull.[3,4] All infants with anencephaly are stillborn or die soon after birth.[1] NTDs may be isolated, one of multiple congenital abnormalities, or a component of a syndrome that is caused by a single-gene disorder, chromosomal abnormality, or teratogenic exposure.[5] Although exact proportions are difficult to estimate, studies suggest that a higher proportion of spina bifida and anencephaly can be classified as isolated, when compared with other forms of NTDs, such as encephalocele or iniencephaly.[6]

Prevalence and Burden of Illness

The Centers for Disease Control and Prevention estimated that the average annual prevalence of anencephaly and spina bifida was 6.5 per 10.000 live births for the period from 2009 to 2011.[7] Estimates of total burden of illness require relying on indirect calculations because fetal deaths and elective terminations attributable to NTDs are underreported. The total number of annual cases from systems without prenatal ascertainment of NTDs for this period is 2,203. Systems with prenatal ascertainment yield a higher estimate of annual cases for the same period at 2,604. The estimated average annual live births for the same period is 4,027,880. Anencephaly accounts for 43 percent of NTDs and is incompatible with life.[7] Infants born with spina bifida can survive with treatment but can have a broad range and degree of disabilities depending on the severity of the defect. Disabilities from spina bifida are based on the level of the lesion and the consequent motor and sensory deficits that occur. Lower lesions are associated with a worse prognosis.

Paralysis, urinary, and fecal incontinence and ventriculomegaly with placement of a ventricular-peritoneal shunt are common complications.

Etiology and Natural History

The neural plate appears during the third week of fetal development and gives rise to the neural folds that fuse in the midline to form the neural tube. Therefore, defects can occur when one or both sites fail to meet and close. Neural tube closure is usually complete by the end of the 4th week after conception.[8]

The etiology of NTDs is believed to be due to a combination of genetic predisposition and environmental influences.[9] The specific environmental influences are still under investigation. NTDs occur more frequently in certain families.[8] Parents with one child with an NTD are at increased risk for having another child with a similar defect (2 to 5%).[10] However, the majority of cases of NTDs occur in families with no prior history of NTDs. It may be that certain individuals with a genetic predisposition have not yet been exposed to the environmental factors necessary to produce an abnormality in their offspring.[11] One of the key environmental influences is the intake of folic acid. Low concentrations of folate may limit methyl groups for DNA replication and methylation. Early evidence suggests that parents with a pregnancy complicated by an NTD are more likely to carry a variant in the gene (677C→T mutation) encoding the enzyme methylenetetra-hydrofolate reductase (MTHFR). MTHFR is an enzyme that regulates folate and homocysteine levels. Individuals who are heterozygous or homozygous for this gene mutation have lower levels of folate, which can decrease the conversion of homocysteine to methionine and may increase the risk of NTDs. A meta-analysis drawn from Dutch and other international sources suggests that the prevalence of the 677C→T is 9.3 percent (95% confidence interval [CI], 8.1 to 10.4%).[12] Estimates for subpopulations in the United States range from 1.2 percent for blacks to 20.7 percent for Hispanics in California, indicating a high degree of variation based on subpopulation.[13] Folic acid may help mitigate the effects of this enzyme mutation, thereby promoting methionine utilization.

Risk Factors

Nonmodifiable risk factors for NTDs include ethnicity, female sex of the neonate, and family history of NTDs in a first- or second-degree relative.[9,14] Evidence indicates that certain racial and ethnic groups appear to be at higher risk for NTDs. Both before and after fortification, birth prevalence rates were highest among Hispanics followed by non-Hispanic whites and non-Hispanic blacks.[15,16] The prevalence of genetic mutations in certain enzymes may differ among these population groups.[17,18] Whether differences between racial and ethnic groups are attributable to genetic or environmental traits is unknown.[19] Folic acid intake from diet is known to vary by ethnicity. For example, Hispanics may be at increased risk for having a baby with NTDs, likely because of lower levels of folic acid in their foods, such as unfortified corn masa products, rather than fortified cereals and pasta.[20-22]

Racial and ethnic differences persist through childhood. In a study of the prevalence of spina bifida among children and adolescents in 10 regions of the United States, the estimate of prevalence for July 1, 2002, was 3.1 per 10,000 (95% CI, 3.0 to 3.3) among non-Hispanic white children and adolescents, 1.9 (95% CI, 1.7 to 2.2) among non-Hispanic black children and adolescents, 3.6 (95% CI, 3.4 to 3.8) among Hispanic children and adolescents, and 1.8 (95% CI, 1.5 to 2.2) among all other children and adolescents.[14] Possible reasons for these differences include differential birth prevalence and survival probability.

Among other risk factors, high maternal body mass index is an independent risk factor for lower serum folate[23] and NTDs.[24] Because as many as 56 percent of women in the United States between the ages of 20 and 39 are overweight or obese, this risk factor is widely relevant to primary care practice.[25] Undiagnosed and pregestational (type 1 or type 2) diabetes also serve as risk factors for NTDs.[26,27] In addition, women with epilepsy who take certain antiepileptic medications, such as valproic acid or carbamazepine, are at increased risk of spina bifida (1 to 2% and 0.5%, respectively).[28] Another medication associated with NTDs is Warfarin.[29] Malabsorption of micronutrients including dietary folate (e.g., from bariatric surgery)[30] or maternal heat exposure (sauna, hot tub, fever, or electric blanket)[31] also elevate the risk of NTDs.

A study of the proportion of NTDs attributable to known risk factors, modifiable or otherwise, found that the factors responsible for the greatest proportion of cases included maternal Hispanic ethnicity, obesity, low dietary folate intake, female infant sex, and lack of folic acid supplementation.[9]

Prevention

Rationale for Intervention

NTDs are the second most common congenital major anomaly in the United States, second only to cardiac malformations. NTDs occur very early in the pregnancy, with no or only limited chance for complete recovery. Prevention is the only medical solution. Periconceptional folic acid supplementation is a primary prevention intervention that can be implemented in primary care settings.

Often used interchangeably, the term *folate* refers to the water-soluble B vitamin (B9) that occurs naturally in foods, while *folic acid* is the term applied to the synthetic form of folate that is found in supplements and added to fortified foods. Folic acid supplementation is usually provided as part of a single or multivitamin.

Intervention Strategies

The main approaches to achieving adequate folate concentrations in women who are capable of becoming pregnant in the United States are ensuring a healthy diet that includes foods fortified with folic acid, providing folic acid supplements, and providing a combination of supplements and a folic acid-rich diet.[32] Although other risk factors for NTDs exist, such as diabetes, obesity, and family history, prevention measures have focused primarily on promoting folic acid consumption through diet and supplements.

In 1998, the U.S. Food and Drug Administration required the addition of folic acid to all enriched cereal grain products sold in the United States.[33] The rate of NTDs has dropped since food fortification laws were implemented.[7,16,34,35]

Dietary Measures and Biomarkers of Folic Acid Intake

Several measures are used to assess the adequacy of dietary folic acid consumption: recommended daily allowance (RDA), dietary folic equivalent (DFE), and estimated average requirement (see Table 1).

Another approach is to look at red blood cell (RBC) or serum folate concentrations as a biomarker for folic consumption. Plasma or serum concentrations of folate reflect transient levels of folate found in circulation. RBC concentrations are thought to be a more accurate measure

because it reflects body stores of folate. There is no stated threshold value for plasma or serum concentrations to determine deficiency as it relates to the risk of NTD. The World Health Organization recommends an RBC folate concentration above 400 ng/ML (906 nmol/L) in women of reproductive age to achieve the greatest reduction of NTDs.[36] Although folate concentrations have traditionally been assessed using microbiological assays, newer assays are being developed but are not yet standardized. Consequently, current assays do not produce comparable results and may lead to inaccurate assessments of folate status. Folate status reflects both dietary intake and absorption. The question of how much natural food folate or folic acid intake is necessary to achieve adequate RBC folate concentrations has not been resolved yet.[36,37]

Sources of Folate and Folic Acid

Women can consume folate by eating foods rich in folate such as dark green leafy vegetables, oranges, orange juice, and legumes. Women can consume folic acid, the synthetic derivative of folate, by either eating food fortified with folic acid such as cereals, grains, and pasta products or by taking a dietary supplement or multivitamin containing folic acid of varying doses. Manufacturers are mandated by law in the United States to fortify cereal grain products (e.g., grains and pastas) that are labeled as "enriched"—a mandatory addition of folic acid at 0.14 mg per 100 g of grain product. Other cereals and related products such as ready-to-eat cereals may be voluntarily fortified, but their folic acid content can change because the level is not mandated.

It is important to note that the bioavailability of naturally occurring food folate is lower than folic acid. Since the 1998 Food and Drug Administration national requirement to fortify enriched cereal grain products, the national incidence of babies born with NTDs has decreased.[7,16,34,35] However, it remains challenging for most women to consume the daily requirement of 0.4 mg from diet alone. U.S. women age19 years or older have a median daily intake of 0.117 mg of folic acid per day from mandatorily fortified food.[38] Data from the 2007 to 2012 National Health and Nutrition Examination Survey (NHANES) suggest that 48.4 percent of U.S. women of childbearing age (95% CI, 46.3 to 50.6) reported consuming folic acid from mandatorily fortified foods only.[39] In another study of pregnant women in North Carolina (n=2,247), only 60 percent met folic acid recommendations from diet alone.[40] Additionally populations that do not consume mandatorily fortified foods (e.g., those on gluten-free or Atkins diets) are not protected by mandatory food fortification.

Folic acid from diet varies by ethnicity. Some investigators reported on the decreased dietary folic acid intake among in U.S. Mexican-American women who may be at increased risk because of lower levels of consumption of fortified foods such as cereals and pastas as a result of their corn masa-based diets.[20-22] Dietary supplements, including multivitamins, contain large amounts of folic acid, and U.S. adults commonly use supplements.[41] Supplements containing folic acid in the United States generally contain 400 to 800 micrograms of folic acid. However, doses up to 1,000 micrograms are permitted without a prescription.

More than 28 percent of 2007 to 2012 NHANES participants reported using a dietary supplement containing folic acid (over 71% not taking folic acid daily). [39] Of those who took a supplement containing folic acid, about half (14.6 % of all women) took supplements that contained less than the daily recommended dose of 400 µg. [39] PRAMS data for 2009 report that only 30 percent of women reported taking a multivitamin, prenatal vitamin, or folic acid supplement daily 1 month before conception (70% were not taking folic acid daily).[43]

Blood folate data from NHANES have documented improvements in the folate status of the U.S. population after fortification was implemented.[44] The prevalence of low serum folate (<10 nmol/L) among U.S. women of childbearing age (ages 15 to 44) declined from 32.2 percent in the prefortification period (1988 to 1994) to 5.5 percent in the postfortification period (1999 to 2010). These changes have been accompanied by a decline in the prevalence of NTDs from 10.7 cases per 10,000 live births before fortification (1995 to 1996) to 7.0 after fortification (1999 to 2011).[7] Other countries such as Canada, South Africa, Costa Rica, Chile, Argentina, and Brazil have also reported reductions in the rate of NTDs following the introduction of food fortification.[45]

Consumption of Folate and RBC Folate Concentration

A systematic review and Bayesian meta-analysis explored the question of the extent to which consumption of natural folate translates to increases in RBC and serum folate concentrations. The review excluded studies in settings with folic acid consumption through supplements or fortification that did not include an adequate period of washout.[46] Six studies of nonpregnant, nonlactating females ages 12 to 49 with RBC concentrations assessed with microbiological assay contributed to the analysis. The authors found that a 10 percent increase in natural food folate intake can increase RBC folate concentrations by approximately 6 percent (95% Credible Interval [CrI], 4% to 9%). Using the model, the authors estimated that in a population with a mean natural food folate intake of 450 μg DFE/day, the mean RBC folate concentration would be approximately 1,070 nmol/L (95% CrI, 770, 1,440 nmol/L). For every 10 percent increase in natural food folate intake, the authors reported that serum/plasma folate concentrations could increase by approximately 7 percent (95% CrI, 1% to 12%).

Red Blood Cell Folate Concentration and Neural Tube Defects

Findings from two large epidemiological studies support RBC concentration of folate as a key prevention strategy for NTDs. Daly and colleagues reassessed the findings of a large case-control of pregnant women in Ireland presenting for antenatal care in 3 clinics in Dublin, Ireland, between 1986 and 1990.[47] The investigators analyzed blood samples from 86 cases and 266 controls (normal live births) in a 1:3 ratio for RBC and plasma folate concentrations. Cases and controls were not matched for maternal or gestational age, but both characteristics were similar between the two groups. Median gestational age at the time the samples were collected was 15 weeks. Using an overall NTD rate of 1.9 cases/1,000 births, Daly estimated the risk of NTDs with RBC and plasma folate levels as continuous variables and at different threshold levels. After adjustment for maternal covariates in logistic regression models, dose-response effects were determined for both plasma and RBC folate levels. In assessing RBC folate levels, an eight-fold difference in the risk of NTDs was found among women with RBC concentrations less than 340 nmol/L (150 ng/mL) compared with those with levels of 906 nmol/L (400 ng/mL) or higher ($p< 0.001$). Notably, the study was conducted in a relatively homogeneous population in Ireland. Blood specimens were obtained at a median of 15 gestational weeks, which is well beyond the time of neural tube closure. Thus, the dose-response effects as summarized may not fully reflect the periconceptional relationship between RBC folate concentrations and the risk of NTDs.

In an effort to determine the optional RBC folate concentration to reduce NTDs, Crider and associates[37] reviewed data from two population-based Chinese cohorts prior to food fortification programs: data from over 240,000 participants (1993 to 1995) in a community-based study of folate supplementation[48] (400 ug/day) and 1,194 participants (2003 to 2005) in the population-

based Folic Acid Dosing Trial.[49,50] Nonpregnant women without plans to conceive (intrauterine device in place) were randomized to 1 of 4 dosage regimens: 100 ug/day, 400 ug/day, 4,000 ug/day, or 4,000 ug/week. RBC folate concentrations and MTHFR genotyping was performed at baseline and at 1, 3, and 6 months after supplementation. Crider and colleagues initially analyzed data from the Dosing Trial to assess the association between the length of time that women consumed folic acid supplementation and RBC folate concentrations, adjusted for the presence of the MTHFR genotype. Findings from this initial model were then used to estimate RBC folate concentrations in the community-based cohort based on their report of daily folate supplementation (i.e., pill consumption) in an effort to determine the association between RBC folate concentrations, folate supplementation, and risk of NTDs. Subsequently, the model was applied to U.S. women using published estimates from NHANES. Estimates of the association between RBC folate concentrations and risk of NTDs were consistent with those published in the earlier work by Daly et al. A substantially lower risk of NTDs was seen with RBC concentrations of 1,180 (1,050 to 1,340) nmol/L. Also, similar to Daly, RBC folate concentrations near 1,200 nmol/L were associated with a substantial reduction in NTDS (5.8/10,000 live births). The relative consistency with the earlier estimates by Daly support the potential use of RBC folate concentrations in assessing the risk of NTDs and could inform future health policies. Two distinctly different cohorts were used in the model, but the authors chose a conservative approach, applied estimates from a reliably conducted case-control study, and ultimately used U.S. estimates in the modeling strategy.

Folic Acid Consumption and Pregnancy Intention

Planning or intention to have a baby influences folic acid consumption. Women who plan to get pregnant are more likely to take folic acid prior to becoming pregnant.[51-54] However, half of all pregnancies in the United States are unplanned,[55,56] which presents a challenge in terms of promoting folic acid consumption for women who are not planning to but may become pregnant. Interventions to increase use in this group require messaging to encourage women to take folic acid "just in case" they get pregnant. Alternatively, public health campaigns can promote folic acid use as a method of maintaining good health overall, but these campaigns do not appear to have lowered the prevalence of NTDs.[19] Few studies have assessed which messaging approach is more effective for women who are not intending to but could become pregnant.[57-60] However, formative studies[59,60] suggest targeting messages for planners (women who are planning to become pregnant in the next 2 years) and nonplanners (women who do not plan to become pregnant in the next 2 years). For the latter, messages should be focused on promoting a woman's overall health and well-being and what to do to have a healthy lifestyle (e.g., taking a multivitamin).

Promoting Folic Acid Consumption

Public health campaigns have been effective in increasing awareness, knowledge, and use of folic acid.[61] Although knowledge about the benefits and sources of folic acid increased postcampaign, campaigns have had less effect on women's understanding of the correct timing for taking folic acid supplements.[61] In addition to increasing public folic acid awareness through campaigns, women are increasingly learning about folic acid in the clinical setting. From 1995 to 2008, the proportion of women who reported learning about folic acid from their health care providers increased from 13 percent to 33 percent, according to U.S. national surveys conducted by the March of Dimes.[62] Of women surveyed in 2008, 32 percent reported that their health

provider discussed the benefits of folic acid.[62] However, only 12 percent of women reported that their health care provider advised them that folic acid needs to be taken before pregnancy.[62] Although preconception guidelines from the American Congress of Obstetricians and Gynecologists exist,[63] preconception care has yet to become standard practice of care among health care providers. Providers need to promote and initiate the idea of preconceptional health to help ensure women are as healthy as they can be before they become pregnant.[64]

Current Clinical Practice

Several organizations offer consistent guidance supporting a minimum daily intake of 400 µg per day for women capable of becoming pregnant (Table 2).[65-69] Additionally, some organizations offer an upper level for general populations (800 µg[68] to 1 mg[67]) or recommendations for high-risk populations.[65,67,70,71] High-risk populations include women of Hispanic ethnicities, women expecting a female sex neonate, those who have a family history of NTDs in a first- or second-degree relative, those with high body mass indexes or undiagnosed and pregestational diabetes, women with epilepsy who take certain antiepileptic medications, and women who have low dietary folate intake or currently lack folic acid supplementation.[9]

Previous USPSTF Recommendation

In 2009, the USPSTF recommended that all women planning a pregnancy or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 µg) of folic acid (grade A recommendation). This recommendation was based on convincing evidence from trial and observational evidence from settings without or before food fortification suggesting a reduction in NTDs with doses from 0.4 to 0.8 mg and adequate evidence that folic acid supplementation at usual doses is not associated with harms. The USPSTF also noted that most women in the United States are not ingesting fortified foods at a level thought to provide optimal benefit..

Chapter 2. Methods

Key Questions and Analytic Framework

The investigators, U.S. Preventive Services Task Force (USPSTF) members, and Agency for Healthcare Research and Quality (AHRQ) Medical Officers developed the scope, Key Questions (KQs), and analytic framework (Figure 1) that guided our literature search and review. Specifically, our KQs are:

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

The USPSTF also requested five contextual questions to help inform the report:

1. What is the current intake of folic acid from diet and other sources in women of childbearing age?
2. Does intake of folic acid from diet and other sources differ by pregnancy intention, age, race, ethnicity, and access to foods?
3. Does folic acid supplementation outside of the periconceptional period reduce the risk of neural tube defects?
4. Does the effect of folic acid supplementation in the periconceptional period on neural tube defects differ by medical risk factors (obesity, poorly controlled diabetes, seizure medications, methotrexate or other folate antagonist therapies, and previous pregnancies with neural tube defect)?
5. Are there other potential fetal, neonatal, or maternal benefits from folic acid supplementation in the periconceptional period?

Search Strategies

We searched PubMed/MEDLINE®, the Cochrane Library, and EMBASE for English-language articles published from database inception through January 28, 2016. We used Medical Subject Headings as search terms when available and keywords when appropriate, focusing on terms to describe relevant populations, interventions, outcomes, and study designs. Appendix A describes the complete search strategies. We conducted targeted searches for unpublished literature by searching ClinicalTrials.gov, HSRProj, the World Health Organization's International Clinical Trials Registry Platform, and NIH Reporter. To supplement electronic searches, we reviewed the reference lists of pertinent review articles and studies meeting our inclusion criteria and added all previously unidentified relevant articles. We also manually

reviewed all literature suggested by peer reviewers or public comment respondents and, if appropriate, incorporated it into the final review.

Study Selection

We selected studies on the basis of inclusion and exclusion criteria developed for each KQ based on the PICOTS (population, intervention, comparator, outcome, timing, setting) approach for identifying populations, interventions, comparators, outcomes, timing, settings, and study designs (Appendix B). Appendix C lists excluded studies. We imported all citations identified through searches and other sources into EndNote v.5. Two investigators independently reviewed titles and abstracts. We dually and independently reviewed the full text of abstracts marked for potential inclusion by either reviewer. Two experienced team members then resolved disagreements. We did not apply date limits to our searches and therefore captured all the studies included in the 2009 review.[32] We resolved disagreements by discussion and consensus; if necessary, we sought adjudication of conflicts from other experienced team members.

Population

We included studies that focused on the use of folic acid supplementation for the prevention of NTD-affected pregnancies in women of childbearing age. We did not include studies of prepubertal girls or men or women without the potential for childbearing (e.g., postmenopausal, genetic uterine or ovarian abnormalities).

Interventions

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 (e.g., multivitamin, iron) in combination with folic acid for the prevention of NTDs.

Comparators

For KQs 1a, 1b, and 2a, we included studies that compared interventions with placebo, no treatment, dietary supplementation only, supplementation with prenatal vitamins without folic acid, or iron supplements without folic acid. For KQs 1b, 1c, and 2b, we included studies that compared interventions with lower or higher dose of folic acid supplementation.

Outcomes and Timing

For KQs 1a and 1b, we searched for studies that reported on the benefits of folic acid supplementation initiated before the index pregnancy or in the first trimester to prevent NTDs. For KQs 1c, 2a, and 2b, we searched for studies that reported on the harms of folic acid supplementation initiated before the index pregnancy and during the first, second, and third trimesters of pregnancy.

Settings

For all KQs, we searched for studies conducted in the United States or in countries with very high human development indexes.

Study Designs

For KQs 1a, 1b, and 1c, we included randomized controlled trials (RCTs), controlled trials, cohort studies, case-control studies, and systematic reviews. For KQs 2a and 2b, we included RCTs, controlled trials, cohort studies, case-control studies, systematic reviews, and registry data.

Data Abstraction and Quality Rating

We abstracted pertinent information from each included study; details included methods and patient populations, interventions, comparators, outcomes, timing, settings, and study designs. A second investigator checked all data abstractions for completeness and accuracy. Using predefined criteria developed by the USPSTF and others for additional criteria for diagnostic accuracy studies, two investigators independently assessed the quality of each study as good, fair, or poor (Appendix D).[72] Disagreements were resolved by discussion and consensus. Studies with "fatal flaws" were rated as having high risk of bias (i.e., poor quality). Particular considerations for this topic include 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). We rated studies with one or more of these features as poor quality. Other fatal 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.

Studies in the 2009 Report Meeting Inclusion Criteria

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 Synthesis and Analysis

We qualitatively synthesized findings for each KQ by summarizing the characteristics and results of included studies in tabular or narrative format. To determine whether meta-analyses were appropriate, we assessed the clinical and methodological heterogeneity of the studies following established guidance.[73] We qualitatively assessed the populations, similarities and differences in screening tests or treatments used, and similarities in outcomes and timing of outcomes assessed. We produced forest plots without summary estimates to illustrate patterns of effect size across studies.

Expert Review and Public Comment

This draft report will be reviewed by content experts, USPSTF members, and AHRQ Medical Officers and will be revised based on comments.

USPSTF Involvement

This review was funded by AHRQ. Staff of AHRQ and members of the USPSTF participated in developing the scope of the work and reviewed draft manuscripts, but the authors are solely responsible for the content.

Chapter 3. Results

Literature Search

We identified 5,786 unique records and assessed 757 full texts for eligibility (Figure 2). We excluded 691 studies for various reasons detailed in Appendix C and included 66 published articles (54 studies) of good or fair quality in our main analyses (Appendix D). All five studies[74-78] that were included in the previous review[32,79] were considered for the current review (Appendix E). Of these five studies, three[74-76] were included in our main analyses, one[78] was excluded due to wrong intervention, and one[77] was excluded for high risk of bias. Of the 49 included studies, 20 studies[9,11,20,32,74,75,79-92] addressed KQ 1a, 3 studies[11,75,80] addressed KQ 1b, 8 studies[11,20,75,80,89-92] addressed KQ 1c, 19 articles[32,76,79,81-87,93-101] addressed KQ 2a, and 5 studies[93-95,100,102] addressed KQ 2b. Although we intended to limit studies of harms to folic acid supplementation only, the available evidence was mixed, so we elected to be inclusive and include studies of multivitamins as well. Details of quality assessments of included studies and studies excluded based on poor quality are provided in Appendix D. Appendix F provides additional details on study characteristics.

Results

Key Question 1a: Effect of Folic Acid Supplementation on Neural Tube Defects in Women of Childbearing Age

Overview

We found a total of 20 publications on the question of benefits of folic acid supplementation. Seven publications present results of the only eligible randomized controlled trial (RCT).[81-87] The study, conducted in Hungary, is an RCT that was initiated in 1984 and terminated in 1992, with information collected through 1993. Three publications relate to two cohort studies; one was a Hungarian cohort study of women recruited between 1993 and 1996,[74] and the second was a cohort drawn from women who underwent alphafetoprotein screening or amniocentesis between 1984 and 1987.[90,91] All other studies were case-control studies and compared neural tube defects (NTD) cases to nonmalformed infants[9,11,20,75,80,89] or to infants with non-NTD malformations.[88,92] Additionally, we drew on information from two publications in the previous update.[32,79]

We present information from the RCT first, followed by the cohort studies and the case-control studies. Although the RCT and the cohort studies potentially offer greater controls for potential sources of bias, they predate mandatory food fortification. The case-control studies span a period ranging from 1976 through 2008, including several relying exclusively on data collected after food fortification. Because these eight publications of case-control data draw from related, or in some cases, subsets of the same data, we present them by the broadest data source first (national or multistate followed by two-state or single-state studies), and recency of data collection within each section. Table 3 provides supporting descriptions of each study. Tables 4 and 5 provide results. Because of the heterogeneity across studies and the differences in food fortification over time, we did not pool the results.

Study Characteristics of the Included Randomized Controlled Trial

One RCT, described in seven publications,[81-87] randomized women to a vitamin supplement containing folic acid (0.8 mg folic acid and 12 vitamins, 4 minerals, 3 trace elements) or a trace-element supplement (copper, manganese, zinc, low dose of vitamin C). Women started the supplement at least 28 days before conception and continued at least until the date of the second missed menstrual period.[84] The trial, as part of the Hungarian Optimal Family Planning Programme, excluded women with delayed conception and infertility or with ongoing pregnancies. For the first 4 years, the program also excluded women over the age of 35 or with a prior wanted pregnancy.[83] The trial involved repeated contact with women at regular intervals. Women were asked to visit the clinic immediately after the first missed menstrual period. The staff administered a sensitive serum pregnancy test, followed within 2 weeks by an ultrasound.[86] As a result, the authors note that they had "nearly total ascertainment of unsuccessful pregnancy outcomes, including fetal deaths and malformations."[86, p. 152] The trial included only "informative" cases in the analysis, that is, live births, terminations in the second trimester, and stillbirths (late fetal deaths). It did not account for loss to followup, which constituted 0.9 percent of each arm (26 cases of 2,819 confirmed pregnancies in the multivitamin arm and 23 cases of 2,863 confirmed pregnancies in the trace element arm), or loss due to first trimester losses, chemical pregnancy, ectopic pregnancy, or miscarriage (395 cases, or 14 percent, in the multivitamin arm and 504 cases, or 17.6 percent, in the trace supplement arm).

The trialists ascertained compliance with the supplement by (1) asking women; (2) checking women's record of supplement use, recorded daily with basal body temperatures; and (3) checking boxes of supplements for unused tablets.[83] Women who got pregnant before starting the supplement or during the first month were considered unsupplemented and were referred to prenatal care immediately. Women who got pregnant after a period of supplementation were referred at 12 weeks to prenatal care.

Results of the Included Randomized Controlled Trial

The trial reported no cases of NTDs in the experimental arm and six cases in the control arm. Based on a denominator of "informative" cases only (live births, stillbirths, and second-trimester terminations only; counting each of twin and triplet births separately), the p-value for the Fisher exact test was 0.014. We calculated the Peto odds ratio (OR): 0.131, 95% confidence interval (CI), 0.0263 to 0.648, p=0.013.

Study Characteristics of Included Cohort Studies

At the conclusion of the RCT described above, no additional RCT was considered ethically possible. The authors continued their investigation using the same intervention (multivitamin supplement containing 0.8 mg of folic acid) in women drawn from the Hungarian Periconceptional Service (1993 to 1996), with supplementation provided before conception.[74] The comparison group comprised unsupplemented pregnant women at their first visit in the regional antenatal care clinic between the 8th week and 12th week of gestation; women who were determined (on a one-page personally administered questionnaire) to have taken multivitamins or folic acid supplements during the periconceptional period were excluded. Unexposed women were matched to exposed women on age, socioeconomic status, employment status, and residence during the first year of pregnancy. Informative offspring included malformed fetuses, antenatally diagnosed and terminated in the second or third trimester; stillborn fetuses (late fetal death after the 28th week of gestation and/or weighing >1,000 gm);

and live-born infants. Informative offspring were ascertained in three ways: (1) by antenatal diagnoses of terminated fetuses, supported by a description of pathology; (2) through records at birth; and (3) by examination by a blinded pediatrician at 1 year of age or from pediatricians' records. NTDS included anencephaly and spina bifida. The study had a potential risk of selection bias because women in the supplemented cohort had a higher rate of comorbidities and unsuccessful pregnancies. The latter, in particular, likely prompted them to seek entry into the Hungarian Periconceptional Service. Supplemented women, however, were likely to have planned their pregnancies, had healthier behaviors in the periconceptional period, and received better prenatal care than unsupplemented women.

We also identified an eligible cohort study based on 23,491 women undergoing alpha-fetoprotein screening or amniocentesis between weeks 15 and 20 of gestation (1984 to 1987).[90,91] Most of these women lived in Boston (33%), elsewhere in Massachusetts (48%), elsewhere in New England (5%), and outside New England (14%). Most of the samples were analyzed at the Boston University School of Medicine facilities. Nurses contacted women at the time that their tests were received by the lab; 93 percent did not know the results of their tests at the time of the interview. Nurses then asked women to recall their use of multivitamins in the first 3 months before pregnancy and the first 3 months of pregnancy. Exposure was defined as the use of at least one multivitamin containing folic acid per week, between weeks 1 and 6 following conception. The maximum period of recall was 8 months (3 months prepregnancy and 5 months of pregnancy).

Results of Included Cohort Studies

The Hungarian cohort study reported 1 instance of NTD in 3,056 supplemented women and 9 in 3,056 unsupplemented women.[74] The selection bias arising from higher rates of unsuccessful pregnancies in the supplemented cohort likely biased the results toward the null, while the selection bias from intentional pregnancies likely biased the results toward an effect of the intervention on NTDs. The authors adjusted the odds ratio for birth order, chronic maternal disorder, and history of previous unsuccessful pregnancies. The study reported an adjusted odds ratio (aOR) of 0.11 (95% CI, 0.011 to 0.91, p not reported).

The New England study reported 10 instances of NTDs among 10,713 women who took multivitamins containing folic acid in weeks 1 through 6 compared with 11 instances of NTDs among 3,157 women who did not take any supplements (OR, 0.27; 95% CI, 0.12 to 0.59). By contrast, use of multivitamins containing folic acid from week 7 onward had no statistically significant effect on NTDs (25 in 7,883 vs. 11 in 3,157, OR, 91; 95% CI, 0.45 to 1.80) when compared with nonuse.[90]

Study Characteristics of Case-Control Studies

Data From Multiple States: National Birth Defects Prevention Study

Two included publications used the National Birth Defects Prevention Study. [9,80] The National Birth Defects Prevention Study was established in 1997 and includes 10 population-based birth defects surveillance systems in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. 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.[9] Cases were women with a pregnancy affected by anencephaly or spina bifida that did not result from a single gene or chromosomal abnormality.

Diagnosis from medical records of fetuses or infants were confirmed following review of clinical descriptions and surgery or autopsy reports. A random sample of women from each site who delivered live-born infants without structural birth defects served as controls. Interviews targeted for completion within 6 months of the expected delivery date collected information on dietary and supplement intake, but these could take place no earlier than 6 weeks and no later than 24 months following the expected date of delivery.[9] 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 (24 months postpartum, 9 months of pregnancy, 3 months prepregnancy).

The two publications presented e for the risk of NTDs[9,80] but did not report on the same time period. The more recent of these two publications, from 2013, focused on births from 1997 to 2007 and defined exposure as any use of folic acid, multivitamin, or prenatal vitamin supplement during the month before pregnancy and the first month of pregnancy. The earlier publication, from 2008, focused on births from 1998 to 2003. The authors compared the outcomes of consistent use (taking supplements at least half the number of days, ≥60 days, from 3 months before pregnancy to the first month of pregnancy) with nonuse. The 2008 publication also provided data on outcomes associated with timing of folic acid supplementation (consistent use from 3 months before pregnancy to the first month after pregnancy versus initiating supplement use in the first month of pregnancy).[80]

To avoid double-counting cases and to use the largest potential study, we focus primarily on the 2013 study,[9] with the longer time span, and discuss the 2008 study in the results.[80]

Data From Multiple States: Slone Birth Defects Study

Three included studies draw on the Slone Birth Defects Study and were published in 2011,[11] 2001,[88] and 1993,[92] respectively. The Slone Birth Defects Study began in 1976. It identifies cases, largely from hospital discharge records; randomly selects controls; and identifies 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 has shifted.

The most recent Slone Birth Defects study, published in 2011, identifies cases as arising from discharge records of participating hospitals serving areas surrounding Boston, MA; Philadelphia, PA; San Diego, CA; and Toronto, Canada.[11] Additionally, the study included some cases identified through birth defect registries in Massachusetts and parts of New York state. Nonmalformed controls were selected randomly each month from discharge lists from the same hospitals or from statewide birth records. Not all data sources in the study included fetal deaths and elective terminations of pregnancy.[11] This publication focused on births in the post-food fortification era, from June 1998 to 2008, and defined nonusers as those who use supplements less than 1 day a week or only 2 lunar months before the last menstrual period (LM-2). It compares the effect of supplementation on spina bifida for consistent users (≥ 4 days per week during at least 2 of the 3 periconceptional months, LM-2, LM-1 [one month before the last menstrual period, LM 1 [one month after the last menstrual period]), early pregnancy initiators (≥ 4 days per week beginning in the LM 1 or LM 2 [one month after the last menstrual period]), and inconsistent users (all other use patterns) with nonuse. The maximum period of recall for this study is 17 months (6 months postpartum, 9 months of pregnancy, 2 months prepregnancy).

The 2001 Slone Birth Defects study includes births from 1976 to 1998 in the greater metropolitan areas of Boston, Philadelphia, and Toronto and, between 1983 and 1985, part of the

state of Iowa.[88] The data sources for this study included fetal deaths and elective terminations from 1988 onward. The study defined folic acid supplementation as never, occasional, or daily use in the 2 months after the last menstrual period, but the primary focus of the study was on the effect of exposure to folic acid antagonists in the same 2-month postconceptional period. It compared cases of NTDs (specifically, anencephaly, spina bifida, encephalocele, and other NTDs) with controls having malformations other than NTDs (i.e., hypertrophic pyloric stenosis, indeterminate sex or pseudohermaphroditism, musculoskeletal anomalies of the skull or face, feet deformities, anomalies of the diaphragm, gastroschisis/omphalocele, esophageal stenosis, stenosis of the large intestine or anus, congenital dislocation of the hip, hypospadias, and others). The maximum period of recall for this study was 15 months (6 months postpartum, 9 months of pregnancy).

The 1993 study from the same center evaluated births from 1988 to 1991 in the greater metropolitan Boston, Philadelphia, and Toronto areas.[92] It compared cases (specifically anencephaly, spina bifida, or encephalocele) with controls (specifically other major malformations, such as chromosomal abnormalities, ventricular septal defects, renal defects, transposition of great vessels, hypospadias, limb reduction defects, and craniosynostosis) for the effect of multivitamins. Exposure was defined as daily use of vitamin supplement containing folic acid in the period spanning from 28 days before the last menstrual period to 28 days after, less than daily use in the same period, use of multivitamin with unknown folic acid status anytime in the periconceptional period, and use of a multivitamin with unknown folic acid. The maximum period of recall for this study was 16 months (6 months postpartum, 9 months of pregnancy, 1 month prepregnancy).

We focus on the 2011 study spanning 1998 to 2008[11] in the analysis because it is consistent with other studies in comparing NTD cases with nonmalformed controls. We also discuss and compare the results of the 2001 study[88] and the 1993 study in the results.[92]

Single-State or Two-State Data Sources

The most recent study from a more 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 (including live births, stillbirths, spontaneous abortions, and elective terminations) and 158 control women with normal live births.[20] NTDs included anencephaly, spina bifida, and encephalocele. Cases were ascertained using the Texas Department of Health's Neural Tube Defect Project, which relied on prospective case finding through hospitals, birthing centers, ultrasound centers, abortion centers, and midwives. Control women were randomly selected residents of the study area with normal births during the same time period. Exposure was defined as daily use in every month in the preconception period (≤ 3 months before conception), any reported use, or postconception use (≤ 3 months before conception). Interviews were conducted approximately 1 month postpartum. The average period of recall for this study was 13 months (1 month postpartum, 9 months of pregnancy, 1 month prepregnancy).

A case-control study drew on cases from the California Birth Defects Monitoring Program. These cases included singleton fetuses and live-birth infants diagnosed with an NTD (anencephaly, spina bifida, and other [combined anencephaly and spina bifida, craniorrhachischisis, and iniencephaly]) between June 1989 and May 1991 and electively terminated NTD fetuses from February 1989 and January 1991. The study identified cases randomly from area hospitals, drawing from each in proportion to the hospital's contribution to the total population of infants born alive.[75] The study was able to reach 549 (88.0% of 624

eligible case mothers and 540 (88.2% of 612 eligible control mothers. Exposure was defined as any use in the 3 months before conception or the 3 months after conception. Additionally, the study estimated, based on self-reports of composition and frequency of use, the average daily folic acid supplement intake from all supplements: <0.4 mg, 0–4 to 0.9 mg, and ≥1.0 mg. Interviews were conducted on average 5 months after birth, leading to an average recall period of 17 months (5 months postpartum, 9 months of pregnancy, 3 months prepregnancy).

An older case-control study drew from cases identified in California and Illinois between 1985 and 1987 (the National Institute of Child Health and Human Development [NICHD] Neural Tube Defects Study).[89] The authors included anencephaly, meningocele, myelomengocele, encephalocelen, rachischisis, iniencephaly, and lipomeningocele in their definition of cases. In California, cases were identified through a state-mandated reporting systems for NTDs or through contracts with ultrasound, amniocentesis centers, disability services, and parents' support groups. In Illinois, cases were identified through ultrasound and genetic units, perinatal networks, hospital neurosurgery services, and vital records. Controls were matched for race or ethnicity, gestational age at diagnosis, date of diagnosis, and geographic area. In California, cases were matched by zip code, and in Illinois, they were matched by county. Exposure was defined as the recommended daily allowance (RDA) or more (that is, women took supplements containing the RDA of at least four vitamins or a higher dose at least 6 days per week), less than the recommended daily allowance, and none. The authors calculated the amount of folate received based on direct reports of brand-name supplements. Interviews were conducted no more than 3 months after birth, leading to a maximum recall period of 13 months (1 month postpartum, 9 months of pregnancy, 3 months prepregnancy).

Results of Included Case-Control Studies

Despite differences in definition of exposure, comparison, and timing across the two National Birth Defects Prevention Study publications examining the effect of folic acid supplementation on NTDs, both publications are consistent in demonstrating a lack of effect of folic acid supplementation on benefits (aOR for anencephaly and spina bifida, 0.93; [95% CI, 0.82 to 1.06]; and 1.2 for anencephaly [95% CI, 0.8 to 1.9], respectively).[9,80] A potential explanation for the findings from this surveillance-based database is that in the post-food fortification era, the majority of cases of NTD arising from folate deficiency have been averted, and the remainder of the cases represent other potential etiologies. A second explanation is that these findings could have arisen from bias. The National Birth Defects Prevention Study is a surveillance-based database in which 8 of 10 sites record fetal deaths and elective pregnancy terminations in addition to live births. This case ascertainment approach mitigates the risk of bias from selection that otherwise occurs in studies focusing on live births only, where potentially eligible cases (i.e., fetal deaths and elective pregnancy terminations attributable to NTDs) are lost to analyses. If folic acid supplementation is protective, a sample that is selectively missing women who do not use folic acid supplements and have NTD-affected pregnancies that end in terminations or stillbirths will have higher odds of NTDs with folic acid supplementation than a sample without selection bias. The risk of recall bias, however, is a concern with all retrospective studies. An additional risk of differential recall bias may occur if study participants are generally aware of the potential benefits of folic acid and case mothers systematically overreport its use. A "yes/no" categorization of folic acid supplementation further risks misclassifying exposure.[9] One publication attempted to address recall bias by focusing on consistent use,[80] but the risks stemming recall over the course of up to 3 years persist.

The 2011 Slone Birth Defects Study found no effect of folic acid supplementation on the risk of spina bifida, regardless of the level of supplementation. Consistent users, when compared with nonusers, had an adjusted odds of 1.11 (95% CI, 0.74 to 1.65). Early pregnancy initiators had an adjusted odds of 0.79 (95% CI, 0.54 to 1.16). Inconsistent users had an odds of 2.20 (95% CI, 0.64 to 7.62). These results could be explained by the ceiling effect: all cases of NTDs preventable through supplementation were averted by food fortification and the remainder constitute a population with a different etiology. Alternatively, these results could arise from bias. Specifically, the sources of bias include (1) differential recall of supplementation, particularly in an era with more widespread knowledge of the support and claims for the use of folic acid supplementation in pregnancy and (2) selection bias from incomplete case ascertainment because the study did not consistently include terminated spina bifida cases, which were available consistently from only one site.

The two pre-food fortification Slone Birth Defect studies with overlapping time periods consistently demonstrate that daily use of supplements reduces the risk of NTDs compared with nonuse (aOR of 0.7; 95% CI, 0.5 to 0.8 in the 2001 study;[88] adjusted relative risk of 0.6; 95% CI, 0.4 to 0.8 in the 1993 study[92]). The Slone Birth Defect study, particularly in the early years, had a potential risk of selection bias by not including stillbirths and elective abortions. Later rounds of analysis included a more complete case ascertainment process. The risks of recall bias were somewhat mitigated by having a shorter recall period and a calendar aid highlighting the woman's last menstrual period. Additionally, these two studies attempted to correct for the issue of differential recall of periconceptional exposure in cases and controls[88,92] by comparing cases of NTDs with controls of other malformed infants. The 1993 found a much higher rate of knowledge of the folic acid hypothesis among NTD case mothers than among control mothers of other malformed infants (74/432 [17%] vs. 65/2,561 [2.5%]), suggesting that the knowledge of the hypothesis could skew recollections of folic acid supplement intake.[92] However, all cases in this study belong in the pre-food fortification era and do not address the effect of folic acid supplementation in the current environment.

Notably, the 2001 study also offered, through the analysis of the effect of folic-acid antagonists, a perspective on what would occur when women are folate deficient because of a folate antagonist. The study found that the adjusted odds of NTDs among women exposed to folic acid antagonists was 2.8 (95% CI, 1.7 to 4.6).

The study of Mexican-Americans, spanning the pre- and post-food fortification era, found a nonsignificant reduction in the odds of NTDs associated with daily consumption of multivitamins containing folic acid (0.77; 95% CI, 0.19 to 3.22); 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 to 5.78; p not reported).[20] Of note is the extremely low levels of folic acid supplement use in both arms (3 cases of daily use in the 3-month preconceptional period versus 66 of no use in the 6-month periconceptional period among cases; 4 cases of daily use in the 3-month preconceptional period versus 68 of no use in the 6-month periconceptional period among controls).

Two other studies were conducted in the pre-food fortification era. Both studies drew on data from the California Birth Defects Monitoring program, using cases from 1989 to 1991,[75] and 1985 to 1987. The Shaw et al. study found an OR of 0.65 (95% CI, 0.45 to 0.94) for any use in the 3 months before conception. A larger analysis comprising women reporting supplement use in the 3 months before and 3 months after conception found an OR of 0.6 (95% CI, 0.46 to 0.79). The NICHD Neural Tube Defects Study, using a combination of slightly older California data

(1985 to 1987) and Illinois data (also from 1985 to 1987), reported no effect of supplements on NTDs (calculated OR, 1.00; 95% CI, 0.73 to 1.40; p=0.97).[89] The Shaw et al. study was able to ascertain the status of approximately 88 percent of eligible cases and controls.[75] By contrast, the case ascertainment of the Mills et al. was estimated, based on a re-evaluation of the likely prevalence, to be as low as 43 percent.[75]

Key Question 1b: Variation in Effect of Folic Acid Supplementation by Race and Ethnicity

Study Characteristics

Three case-control studies provide limited information about the effects of folic acid supplementation by racial, ethnic, and other maternal characteristics.[11,75,80] Table 3 presents study characteristics and Table 6 provides results. The Slone Birth Defects Study provides the most recent data (1998 to 2008).[11] In this study, mothers of infants with and without birth defects were interviewed within 6 months of delivery about pregnancy exposures, including details of diet and vitamin intake. Periconceptional folic acid supplementation and dietary folate consumption were compared between 205 mothers of spina bifida cases and 6,357 mothers of nonmalformed controls. Women who reported folic acid supplement use > 4 days per week during at least 2 of the 3 periconceptional months (2 months before to 2 months after last menstrual period) were considered to be "consistent users." A second case control study analyzed the data from 1998 to 2003 from the National Birth Defects Prevention Study.[80] It used logistic regression to compute crude and aORs between cases and controls assessing maternal periconceptional use of folic acid supplements and intake of dietary folic acid. The third case-control study used data from the California Birth Defects Monitoring Program (1989 to 1991). Mothers of 549 cases and 540 controls were interviewed about vitamin supplements used in the 3 months before or 3 months after conception.[75]

Results

The Slone Birth Defects study found that in the setting of folic acid fortification, folic acid supplementation does not appear to offer further benefit for reducing spina bifida risk.[11] Women who reported taking folic acid supplements at least 4 days per week during the months before neural tube closure did not have decreased risk of spina bifida compared with women who reported no supplementation. The lack of protective relationship was observed for white women. The study found a possible increased risk of spina bifida among consistent supplement users of Hispanic ethnicity when compared with nonusers (aOR, 2.20; 95% CI, 0.98 to 4.92); however, the authors note this finding may be due to chance.

The National Birth Defects Prevention Study found that periconceptional supplement use did not reduce the 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.[80] Supplement use-race interactions were not significant for anencephaly (p=0.57) or spina bifida (p=0.08). However, the authors note that counts among non-Hispanic black and Hispanic populations were relatively small, so findings should be interpreted with caution.

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.[75] Reduction in risk for Hispanics was of smaller magnitude (OR, 0.96; 95% CI, 0.44 to 2.10) than that observed for non-Hispanic whites (OR, 0.62; 95% CI, 0.35 to

1.10) and blacks (OR, 0.54; 95% CI, 0.09 to 3. 20), but these results were not statistically significant and could have occurred due to chance.

Although a study focusing on Mexican Americans[20] does not provide information about *differences* by race/ethnicity, it provides an estimate of effect among Hispanic women, albeit in a limited geographical context. When adjusted for maternal age, education, obesity, and previous stillbirth or miscarriage, the OR was 1.12; 95% CI, 0.22 to 5.78, p not reported).

Key Question 1c: Variation in Effect of Folic Acid Supplementation by Dosage, Timing, and Duration of Therapy

Study Characteristics

One cohort study, set in New England (1984 to 1987) and described in two publications,[90,91] and six case-control studies[11,20,75,80,89,92] provided information on dosage and timing of folic acid supplementation on NTDs. Of these, the most recent case-control studies drew from the Slone Birth Defects Study (1998 to 2008)[11] and the National Birth Defects Prevention Study (1998 to 2003).[80] A third, focusing on Mexican Americans along the Texas-Mexico border, was conducted between 1995 and 1999.[20] Two older case-control studies drew from the California Birth Defects Monitoring Program (1989 to 1991)[75] and the Slone Birth Defects Study (1988 to 1991),[92] respectively. The oldest case-control study, the NICHD Neural Tube Defects study, drew from both California and Illinois (1985 to 1987).[89] Four studies (1 cohort[91] and 3 case-control studies[75,89,92]) reported on dose of folic acid supplementation. Five studies (1 cohort[90] and 4 case-control studies[11,20,75,80]) reported on timing of folic acid supplementation.

Table 3 provides further details on study characteristics. We report the cohort study first and then report on the case-control studies in order of recency.

Study Results: Folic Acid Supplementation Variation by Dosage

All included studies on dose predate the food-fortification era (Table 7). The New England cohort study (1984 to 1987)[91] found no statistically significant differences by dose (1 to 399 dietary folate equivalents [DFEs] from supplements, 400–799 DFEs, and ≥800 DFEs versus none). Although authors infer that the study provides no evidence of a dose-response relationship, the number of NTDs for each dose category was low.

The case-control study using data from the California Birth Defects Monitoring Program compared the effect of three levels of dose (<0.4 mg, 0.4 to 0.9 mg, and ≥1.0 mg) with no folic acid supplementation in the 3 months before or after conception.[75] The study found no differences by dose for women reporting use in the 3 months before conception. In a larger sample of women reporting use in the 3 months after conception (including those who started before conception and continued), doses below 0.4 mg or above 0.9 were not statistically significant when compared with no use (OR, for 0.4 mg: 0.99; 95% CI, 0.56 to 1.80; OR for ≥1.0: 0.92; 95% CI, 0.54 to 1.60); only the use of 0.4–0.9 mg had a statistically significant effect on NTDs when compared with nonuse (OR, 0.54; 95% CI, 0.41 to 0.72). Of note, however, is the small sample size for the higher and lower doses (54 cases and controls with <0.4 mg, 75 cases and controls with ≥1.0 mg).

Data from the Slone Birth Defects Study (1988 to 1991)[92] suggest lower odds for daily use versus less than daily use on NTDs (calculated OR, 0.57; 95% CI, 0.35 to 0.93). A supplemental analysis in the same study of differences by dosage among women who did not know the hypothesis between folic acid supplementation and NTDs failed to find a dose-response effect.

An older case-control, the NICHD Neural Tube Defects Study, drawing from cases identified in California and Illinois between 1985 and 1987, reported on the number of NTDs in those with the RDA from supplements compared with those with less than the RDA.[89] The study reported no statistically significant differences between different levels of exposure (calculated OR, 1.84; 95% CI, 0.92 to 3.71). Of note, this study likely had problems with case ascertainment.

Study Results: Folic Acid Supplementation Variation by Timing

The single cohort study (drawing on cases from 1984 to 1987 and set in New England[90]) reported that using multivitamins in weeks 1 through 6 resulted in a lower odds of NTDs than using multivitamins in weeks 7 and later (10 of 10,731 vs. 25 of 7,795 calculated OR, 0.29; 95% CI, 0.14 to 0.60) (Table 8).

Of the four case-control studies, two were set in the post-food fortification era,[11,80] one spanned the pre- and postfortification era,[20] and one predated the food-fortification era.[75] The most recent case control study[11] reported the risk of consistent use (defined as 4 or more days of use per week in 2 of 3 periconceptional months) versus initiating use in the first month of pregnancy (more or more days per week starting in the first or second month postconception). Consistent users had a higher but statistically nonsignificant risk of spina bifida (calculated OR, 1.23; 95% CI, 0.88 to 1.73). The second postfortification case-control study[80] reported the risk of anencephaly and spina bifida separately. Women who started folic acid supplementation use before pregnancy had a lower risk of anencephaly when compared with women who started during the first month of pregnancy (calculated OR, 0.61; 95% CI, 0.40 to 0.93). No difference was found for the spina bifida cases (calculated OR, 0.95; 95% CI, 0.71 to 1.28).

A study of Mexican-American women along the Texas-Mexico border, drawing from cases from 1995 to 1999, did not find any statistically significant differences in the odds of NTDs by preconceptional versus postconceptional use (calculated OR, 1.84; 95% CI, 0.58 to 5.86).[20]

The case-control study using data from the California Birth Defects Monitoring Program (1989 to 1991) found lower odds but wide confidence intervals for the use of folic acid supplements in the 3 months before conception when compared with no use. It also found no statistically significant effect of NTDs compared with any use of folic acid supplements in the 3 months after conception (88 cases and 98 controls in 3 months before conception versus 322 cases and 384 controls after conception; calculated OR, 1.07; 95% CI, 0.77 to 1.48).[75]

Key Question 2a: Harms of Folic Acid Supplementation in Women of Childbearing Age

Study Characteristics

We included one RCT comparing folic acid supplementation with a multivitamin to trace elements described in seven publications[81-87] and one cohort study (Table 9).[76] Additionally, the previous review also reported on twinning.[32,79,81-83,86,87] The trial characteristics are described under KQ 1a.[94] As noted previously, the trial included only "informative" cases in the analysis (i.e., live births and stillbirths [late fetal deaths]). The authors noted that it was generally not possible to recognize multiple pregnancies in miscarriages or ectopic pregnancies.

In a retrospective, population-based cohort study in Norway (N=176,042) of births from December 1998 through the end of 2001,[76] the use of folic acid supplements and multivitamins was ascertained using a birth notification form submitted through the Norway Birth Registry. For

multiples, the registry received one form for each birth. Separate notification was made for pregnancies conceived through in vitro fertilization.

Two meta-analyses[94,101] met our initial inclusion criteria and evaluated the effects of periconceptional folic acid supplementation on childhood respiratory illness (Table 10). One meta-analysis[94] with a low risk of bias evaluated the association of folic acid supplementation during the specified time frame of 1 month prior to pregnancy or during the first 12 weeks of pregnancy with childhood asthma or wheezing and allergy-related outcomes. However, because of heterogeneity in the type of folic acid supplementation (e.g., folate, combination of folate and dietary folate) and measure of exposure during the periconceptional period, authors limited the pooled estimate to five studies (three cohort; two nested case control)[95-99] that assessed folic acid in the periconceptional period (from the month prior to pregnancy) or first trimester. Folic acid supplementation was operationalized as folic acid supplementation (yes/no). In the three studies that reported the dose of folic acid, the range was 400 to 600 µg/day.[96-98] In one study, the average dose was not reported, but the investigators suggested that the dose was 400 µg/day.[95] Asthma or wheezing was assessed through a structured parental interview or parental completion of a medical questionnaire. Two studies reported on asthma,[98,99] two studies reported on wheezing,[95,96] and one study reported on wheezing and asthma.[97]

A second meta-analysis,[101] rated as medium risk of bias, included five published studies and data from a review of a longitudinal cohort study of folic acid supplementation and asthma.

Results

Twinning in Women

In an analysis of informative pregnancies in the trial,[84] the proportion of twin pregnancies and twin births (live and stillbirths) was not statistically significantly different between the multivitamin and trace element arms (Table 11). Out of the total pregnancies in the multivitamin group, 1.9 percent (46/2,421) were determined to be twin gestations compared with 1.36 percent (32/2,346) of pregnancies in the trace element group (X^2, 2.13; p=0.15). The relative risk (1.4; 95% CI, 0.97 to 2.25) was not statistically significantly different between the two groups. The proportion of twin *births* (as opposed to *pregnancie*s) was higher in the multivitamin group (93/2,468; 3.77%) than in the trace element group (64/2,378; 2.69% relative risk [RR], 1.42; 95% CI, 1.01 to 1.98).

In a subsequent analysis for the same trial, those who were not supplemented were excluded (that is, women who got pregnant before or during the first month of supplementation). The analysis continued to demonstrate a lack of significant difference in relative risk of twin pregnancies (RR, 1.5; 95% CI, 0.98 to 2.38). The study found an increased risk of twin births in the multivitamin group compared with the trace element group (RR, 1.5; 95% CI, 1.09 to 2.08). The increased risk in the multivitamin group may be due to several factors, including differences in maternal characteristics and pregnancy-specific or delivery-related complications. Limited information is available on differences in maternal characteristics and essentially no data are available on pregnancy-related factors. The findings should be interpreted with caution because births include live births and stillbirths, and there are no data to discern the proportion of live or stillbirths in each treatment arm.

Twinning and Ovarian Stimulation in Women

The Hungarian trial did not find evidence[84] for an increased risk of twinning among women receiving fertility treatments and randomized to a multivitamin or trace element. The proportion of women in the multivitamin group and trace element group who received fertility treatment was similar at 6.4 percent and 6.6 percent, respectively. Among the 2,198 women who received multivitamin supplementation, 141 received clomiphene citrate with or without other infertility drugs and 19/141 (13.5%) resulted in a multiple gestation. Of the 2,057 women in the multivitamin group who did not receive fertility drugs, 25/2,057 (1.2%) resulted in a multiple gestation. Among the 2,170 pregnancies that received trace elements, 143 underwent ovarian stimulation and 12/143 (8.4% resulted in a multiple gestation. Of the remaining 2,027 conceived without ovarian stimulation, 17/2,027 (0.8% twin pregnancies were identified. Among pregnancies that were conceived without ovarian stimulation, the study found no statistically significantly increased risk of twinning among women who received multivitamin supplementation compared with trace elements (RR, 1.45; 95% CI, 0.78 to 2.68). Among women who underwent ovarian stimulation, the relative risk of twinning in those receiving multivitamins was calculated to be 1.6; 95% CI, 0.81 to 3.18. The point estimates and wide confidence intervals are largely due to the relatively small total number of twin gestations in this subgroup analysis (n=73) and the similarly small number (proportion) of twin gestations in the multivitamin and the trace element groups.

The initial analysis of the cohort study[76] found an increased odds (baseline adjustment for maternal age and parity) of twinning among pregnancies with folate use compared with those with no folate supplementation.. With further adjustment for in vitro fertilization, the odds ratio was attenuated and no longer statistically significant (1.04; 95% CI, 0.91 to 1.18).

In analyses stratified by method of conception (in vitro fertilization or natural conception), the odds of twinning with folic acid supplement use in natural conception (OR, 1.13; 95% CI, 0.97 to 1.33) were slightly higher than the odds of twinning with folic acid use supplement in in vitro fertilization (OR, 0.90; 95% CI, 0.73 to 1.11). In an analysis stratified by parity, women with no prior pregnancies had slightly higher odds of twinning with folic acid supplement use (OR, 1.31; 95% CI, 1.05 to 1.62). In a subsequent modeling analysis, the authors assumed that 12.7 percent of true in vitro fertilization was misclassified as natural conception and that 45 percent of women were misclassified as folic acid supplement users. Authors found an attenuated effect of folate and multivitamins before pregnancy after adjusting for age, parity, and potential misclassification; neither was statistically significant (OR for folic acid supplements before pregnancy: 1.02; 95% CI, 0.85 to 1.24; OR for multivitamins before pregnancy: 0.98; 95% CI, 0.83 to 1.17). The authors found elevated risks of twinning with folic acid supplement (OR, 1.14; 95% CI, 1.00 to 1.23) or multivitamin use (OR, 1.30; 95% CI, 1.14 to 1.49) during pregnancy after adjusting for age and parity. The authors note, however, that this effect could be explained by confounding by indication, that is, an increased use of folic acid or multivitamin supplements once the multiple gestation is recognized.

Childhood Asthma or Wheezing and Allergen-Related Outcomes

We identified six eligible articles,[93,96-99,102] which were synthesized in two systematic reviews.[94,101] All included primary studies were observational with attendant risks of misclassification and recall bias. We discuss pooled estimates from the meta-analyses below (Table 12). With regard to asthma, the pooled estimate from one meta-analysis[94] focusing on the prepregnancy period through the first trimester (N not reported) found no evidence from three

studies[97-99] of an association between maternal folic acid supplementation compared with no use and childhood asthma, with pooled relative risk of 1.01 (95% CI, 0.78 to 1.30; p=0.95; I^2=0.00; p=0.73).[94] For the combined outcomes of wheezing in infants and toddlers and asthma in children, the pooled estimate from five studies[95-99] resulted in a slightly elevated risk for the use of folic acid supplements before pregnancy or during the first trimester (RR, 1.05; 95% CI, 1.02 to 1.09; p=0.01; I^2=0.00; p=0.68).

A second meta-analysis evaluating any exposure from the periconceptional period through pregnancy (n=14,438)[101] included five studies in the pooled estimate.[93,97-100] The meta-analysis found no association between folic acid supplementation during the periconceptional period or pregnancy and the development of child asthma (OR, 1.06; 95% CI, 0.99 to 1.14), but the authors reported wide variations in the dose of folic acid supplementation across included studies. Other allergen-related outcomes included a combination of atopy, eczema, and atopic dermatitis. One meta-analysis[94] evaluated these outcomes for periconceptional and first trimester exposure from four studies[95-97,100,103] and found two elevated reports of risk from one study[95,96] among 13 reported associations of lower respiratory tract infections (adjusted RR, 1.09; 95% CI, 1.01 to 1.15) and hospitalizations from lower respiratory tract infections (adjusted RR, 1.24; 95% CI, 1.09 to 1.41) among infants 0 to 18 months.

Other Reported Harms in Women

The Hungarian trial also reported on other harms.[86] The presence or absence of these harms represents potential side effects of folic acid supplementation, many of which are common pregnancy symptoms, and provides reassurance of the safety of folic acid supplementation in the preconceptional period. The Hungarian trial[86] reported on differences between weight gain; body weight; gastrointestinal symptoms (hunger or increased appetite, lack of appetite, heartburn and indigestion, constipation, diarrhea, irregular and/or colic defecation [urge to defecate after a meal]); and exanthema, a skin disorder characterized by a rash and skin eruptions, after periconceptional multivitamin and trace element supplementation (Figure 3). The study found no statistically significant differences in the report of most of these symptoms between the two groups from before pregnancy through pregnancy confirmation. Women who continued supplementation through the first 12 weeks of pregnancy had an increased risk of weight gain (calculated RR, 1.78; 95% CI, 1.23 to 2.57), diarrhea (calculated RR, 7.09; 95% CI, 2.72 to 18.47), and constipation (calculated RR, 1.67; 95% CI, 1.06 to 2.63) when compared with the trace element group. They also had a lower risk of irregular and/or colic defecation when compared with the trace element group (RR, 0.33; 95% CI, 0.16 to 0.68). The study found no difference in the risk of exanthema, although two participants in the multivitamin and one in the trace element group withdrew from the study because of this disorder.

Key Question 2b: Variation in Harms of Folic Acid Supplementation by Dose, Timing, and Duration of Therapy

Study Characteristics

One meta-analysis[94] with a low risk of bias evaluated the association of folic acid supplementation with childhood asthma or wheezing and allergy-related outcomes. Studies were grouped by the timing of folate exposure: early (preconceptional, periconceptional, first trimester) compared with late (second and third trimesters).[93,95,100] The same meta-analysis found one study reporting on dose (<200 µg/day, 200 to 499 µg/day, and >500 µg/day).[102]

Results

As noted in KQ 2, the meta-analysis that analyzed folic acid supplement use as a dichotomous variable and reported its association with asthma in childhood showed a pooled estimate of RR of 1.01 (95% CI, 0.78 to 1.30; p=0.95; I^2=0.00, p=0.73; Table 13).[94] Two of the cohort studies included in the meta-analysis examined the association between prenatal use of a supplement containing folic (compared with no use) in the second or third trimester and asthma or wheezing in childhood.[93,95]

Of the 15 associations across two studies, only one association was significantly elevated. Specifically, one study showed that maternal use of folic acid supplements in the third trimester was associated with increased risk of maternal report of wheezing at 1 year (adjusted prevalence ratio, 1.20; 95% CI, 1.04 to 1.39).[93] Regarding other outcomes, three cohort studies examined the use of supplements containing folic acid during the second or third trimester and risk of other allergic outcomes.[93,95,100] The meta-analysis reported no significant findings in 38 reported associations across these three studies.

One study separated the study population into tertiles (<200 mg/day, 200 to 499 mg/day, and >500 mg/day) and compared the second and third tertiles to the first for the incidence of any allergic disease, sensitization, recurrent wheeze, eczema, food reactions, immunoglobin E (IgE) mediated food allergy, and sensitization to food allergens (Table 14). In all cases, the number of cases was small, ranging from 16 to 69. All results had wide confidence intervals spanning or overlapping the line of no difference.[102]

Chapter 4. Discussion

Summary of Evidence

Table 15 provides a summary of findings in this evidence review. This table is organized by Key Question (KQ) and provides a summary of outcomes along with a description of precision, risk of bias, and applicability.

Evidence for Benefits of Folic Acid Supplementation

One randomized controlled trial (RCT), two cohort studies, and eight case-control studies met eligibility criteria, in addition to two publications from the prior review.[32,79] These 20 publications, comprising 11 primary studies and 1 systematic review, drew from 8 data sources (Hungarian trial,[81-87] Hungarian cohort,[74] the New England study,[90,91] the National Birth Defects Prevention Study,[9,80] the Slone Birth Defects Study,[11,88,92] the Texas Department of Health's Neural Tube Defect Project,[20] the California Birth Defects Monitoring Program,[75] and the NICHD Neural Tube Defects Study[89]). Together they span births occurring over three decades, from 1976 through 2007.

After the publication of the Hungarian trial and other trials in women with recurrent neural tube defects (NTDs), the clear evidence of benefit pointed to the need for large-scale public health interventions; the United States added folate to grain products in 1998. The clear evidence of benefit also made the conduct of additional trials unethical. As a consequence, all subsequent studies relied on observational data.

Although all included studies in this review avoid fatal flaws, their designs contain inherent and unavoidable sources of bias. Prospective studies may not be able to ascertain all 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 occurring between 13 months and 3 years prior to the interview. Compounding the risk of recall bias is the relatively widespread knowledge of the protective effective of folic acid supplementation NTDs. Studies that compare cases with NTD malformations with controls with non-NTD malformations may have a lower risk of differential recall bias. Two such studies showed a clear and consistent protective effect of folic acid supplementation but were based on data collected in the prefortification era.[88,92]

Both the risks of bias described above (case ascertainment and recall) will reduce the differences between study groups. A further issue with all designs is the relatively rarity of the outcome and the difficulty of adequately powering studies to determine benefits.

Figures 4 and 5 present the results in a forest plot of the largest or more representative study from each data source. Figure 4 demonstrates that the older studies (with one exception) show a protective effect of folic acid supplementation on NTDs, and the newer studies, all conducted after the introduction of food fortification, do not show a protective effect. The same studies, when sorted by study design (Figure 5), show greater consistency in direction of effect in the cohort studies and greater variation in direction of effect in the case-control studies.

Although the incidence of NTDs has declined in conjunction with food fortification, 23 percent of U.S. women have suboptimal red blood cell (RBC) folate concentrations.[39] Among women who consume supplements, the rate is under 10 percent; among women who do not consume supplements, the rate is 28 percent. Nearly 33 percent of women who consume mandatorily fortified foods alone (i.e., they do not consume folic acid supplements or voluntarily

fortified foods) have suboptimal RBC folate concentrations. These statistics suggest a continued and important role for supplements.

Three case-control studies provide information about the effects of folic acid supplementation by racial, ethnic, and other maternal characteristics.[11,75,80] One study suggested that folic acid supplementation may be less protective for Hispanic women, a second showed a higher risk of NTDs among Hispanic women, and the third did not show an effect. None of the studies are conclusive because of small numbers that could have resulted in chance findings.

One cohort study, set in New England (1984 to 1987) and described in two publications,[90,91] and six case-control studies[11,20,75,80,89,92] provided evidence on dose and timing. All four studies on dose (one cohort[91] and three case-control studies[75,89,92]) predate food fortification; none shows a dose-response effect. Notably, the number of cases for varying levels of dose was small. The five studies (one cohort[90] and four case-control studies[11,20,75,80]) reporting on timing of folic acid supplementation did not consistently compare the same timing of exposure. The two older studies did not find statistically significant effects of folic acid supplementation by timing of supplementation.[20,75] One newer study, conducted entirely in the postfortification era, found more protective effects for women who started before pregnancy when compared with women who started during the first month of pregnancy for anencephaly; the protective effect of early timing of exposure did not appear to hold for spina bifida.[80] The other new study, focusing on spina bifida only, did not find a statistically significant effect of timing of folic acid supplementation on the odds of spina bifida.[11]

Evidence for Harms of Folic Acid Supplementation

We included one RCT comparing folic acid supplementation with a multivitamin to trace elements described in seven publications[81-87] that evaluated the harms of folic acid supplementation in the periconceptional period to prevent NTDs. We also included one good quality cohort study[76] of women with and without that met our inclusion criteria. Although we could not rule out a risk of an increase in higher level multiple gestations (triplets or greater) in the RCT[81-83,86,87] due to a limited number of events, analyses focused on twinning among women with or without treatment with fertility drugs (Clomiphene) were reassuring with point estimates and confidence intervals that did not indicate a risk for multiple gestations. Among a general population of women in the RCT, there was no evidence of a higher risk of twin pregnancies or twin (combination of live- and still-) births. When the analyses were limited to only women who completed full or partial folic acid supplementation, there was no evidence of a higher risk of twin pregnancies. Suggestion of a higher likelihood of twin (live- and still-) births among women with full or partial folic acid supplementation compared with those with full/partial trace elements should be interpreted cautiously given the similarity in point estimate and overlap in the calculated 95% confidence intervals. Findings from the observational study[76] support the findings from the RCT. After adjustment for in vitro fertilization, the authors found no association between periconceptional folic acid supplement use and twinning.

Comparison of maternal symptoms between the multivitamin with folic acid and trace elements groups in the RCT[81-83,86,87] suggested a potential higher risk of maternal weight gain, diarrhea, and constipation at 12 weeks of gestation. These symptoms are common in pregnancy and, thus, limit our ability to draw definitive conclusions about the association of folic acid supplementation and these symptomatic outcomes.

With regard to childhood respiratory illness, two meta-analyses[94,101] provided no evidence of a higher risk of child asthma or other allergen-related illness (e.g., atopy, eczema, and atopic dermatitis) and no consistent variation in these outcomes by timing or dose of exposure.[94]

Applicability of Evidence

Most of the studies included in this review are applicable to primary care. One cohort study of women tested for alphafetoprotein or amniocentesis was representative of older pregnant women, but not all women.[90] The modal age for the cohort study ranged from 30 to 39; by contrast, the average age of women in other studies was in the 20s. A majority of studies reported that they excluded NTD cases with multiple malformations or known syndromal causes of NTDs.

Sufficiency of Intake

Estimates of folate sufficiency of intake vary widely by measure (Table 16). When the highest threshold, the RDA, is used, NHANES data from 2003 to 2006 suggest that only 24 percent of nonpregnant women 15 to 44 years of age consumed the recommended daily intake. Among all women, the median intake of folic acid overall was 245µg, which is less than the recommended amount of 400 µg.[42] Although the proportion of intake varies by race and ethnicity, the proportion of women not consuming the RDA varies from 61 to 74 percent.

Another approach is to set the threshold for insufficiency based on RBC folate concentrations. A threshold of 400 ng/mL or more (906 nmol/L) is based on an association of the threshold with an NTD prevalence of >9 per 10,000 live births. This threshold yields an estimate suggesting a greater level of sufficiency, on average, with 22.8 percent of women having suboptimal RBC folate concentrations for NTD prevention. Levels vary by use of dietary supplements containing folic acid, consumption of mandatorily fortified enriched cereal grain products as their only source of folic acid, non-Hispanic black or Hispanic race and ethnicity, or current smoking status. Among women who consume any supplements containing folic acid, the percentage associated with insufficiency is 9.7; 28 percent of women who do not consume supplements have insufficient RBC folate concentrations.

The estimated average requirement sets the lowest threshold for folate sufficiency, requiring 320 DFEs (based on evidence suggesting that with 320 DFEs half would have RBC folate over 305 nmol/L). NHANES data (2003 to 2006) suggest a much lower level of insufficiency on average: approximately 15 to 19 percent of childbearing-age women (levels vary by age) did not meet the estimated average requirement for folate.

Very few women are exceeding the upper level for folic acid consumptions. According to the 2015 Dietary Guideline Advisory Committee report, which uses NHANES 2007 to 2010 dietary intake data, less than 3 percent of women ages 14 to 50 are getting more than 1,000 ug/day from food, beverages, and dietary supplements.[104]

Variation of Intake From Diet and Other Sources

The National Birth Defects Prevention Study[105] and PRAMS[43,106,107] provide data on folic acid intake (diet and supplemental) prior to pregnancy among women of childbearing age. NHANES,[42] the March of Dimes surveys,[108,109] and other studies provide data on folic acid intake among women of reproductive age overall but do not focus on consumption prior to pregnancy specifically. Across these studies, we found differences in consumption of

supplemental folic acid by age, race and ethnicity, and other characteristics. We also found differences in total folic acid intake—dietary and supplemental.

Differences by Age

Studies consistently found that among women of reproductive age, supplemental folic acid intake increases with age. PRAMS 2009 found that rates of folic acid consumption (multivitamins, prenatal vitamins or a folic acid supplement every day of the month before pregnancy) increased as follows: 42.4 percent among women ages 35 to 55; 34.5 percent among women ages 25 to 34; and 16.1 percent among women ages 18 to 24 ($p<0.05$).[43] The National Birth Defects Prevention Study (1997 to 2005) found rates of compliant folic acid use (defined as 5 or more times per week during the 3 months before conception) as follows: 7.23 percent among women ≤19 years, 16.18 percent among women ages 20 to 24, 39.30 percent among women ages 25 to 34, and 51.96 percent among women ≥35.[105]

The March of Dimes surveys and NHANES also provide data on folic acid consumption among women of reproductive age but do not focus on consumption prior to pregnancy. These studies also found that use of supplemental folic acid increases with age.[42,108,109]

Differences by Race and Ethnicity

Significant improvements in RBC folate status have occurred among all racial and ethnic groups; among non-Hispanic black women, the prevalence of low RBC folate declined from 59.6 percent between 1998 and 1994 to 12.1 percent between 1999 and 2000. During the same time period, the prevalence of low RBC folate declined from 34.5 percent to 4.5 percent among non-Hispanic white women and from 38.7 percent to 1.6 percent among Mexican-American women.[44]

Although all women of childbearing age increased their median total folate intake by at least 100 μg/day since fortification, increases were larger for whites than for blacks and Mexican Americans.[110] White women were also more likely to have reached the 400 μg/day threshold both pre- and postfortification (30 percent and 39 percent, respectively) than black women (20% pre, 26% post) and Mexican-American women (17% pre, 28% post).[110]

Consumption of supplements containing folic acid also varies by race, ethnicity, and other characteristics. According to the 2007 March of Dimes survey, women who were nonwhite, were ages 18 to 24 years, had less than a high school education, or had a household income under $25,000 were the least likely to report daily consumption of a supplement containing folic acid.[111] Studies consistently found that among women of reproductive age, supplemental folic acid intake is higher among whites than blacks and among non-Hispanics than Hispanics. The National Birth Defects Prevention Study found higher rates of compliant folic acid supplement use among white women (43.73%) compared with black (16.89%), Hispanic (10.87%), or other women (27.98%).[105] PRAMS 2009 found that folic acid consumption was highest among white women (34.2%), followed by other (33.0%), Hispanic (22.5%), and black women (19.5%) ($p<0.05$).[43]

The March of Dimes 2008 survey, NHANES,[42] and the California Women's Health Survey[112] found similar patterns by race and ethnicity. NHANES 2003 to 2006 found non-Hispanic whites were most likely to take supplemental folic acid (37.2%), followed by other race/multiracial (24.7%), Mexican Americans (20%), and non-Hispanic blacks (20%).[42] The California Women's Health Survey 2006 found more white women reported daily use of folic acid containing supplements (50.6%) compared with blacks (39.5%) and Asians (40%). Non-

Hispanic women were more likely to report folic acid supplement use (46.9%) than Hispanic women (30.2%).[112]

The March of Dimes conducted a survey of Spanish-language-dominant Hispanic women in 2008. Overall, 21 percent of women took folic acid daily (multivitamins, folic acid supplements, prenatal vitamins). Rates of daily folic acid supplement use varied by ancestry: Mexican (19%), Central American (22%), South American (35%), and Caribbean or other (25%).[109]

Differences by Education

Studies consistently found that the use of supplemental folic acid increases with education. The National Birth Defects Prevention Study found rates of compliant folic acid supplement use as follows: less than high school, 9.04 percent; high school, 17.36 percent; 1 to 3 years of college, 30.98 percent; 4+ years college, 58.20 percent.[105] State-level PRAMS data from Rhode Island[107] and Texas[106] found similar patterns. In Rhode Island (PRAMS 2004 to 2008), daily multivitamin use was as follows: 25.1 percent among women with less than a high school education; 23.1 percent for high school, and 44.5 percent for more than high school ($p<0.0001$). In Texas (PRAMS 2002 to 2010), no daily multivitamin use was highest among women with less than a high school education (80.3%) and high school graduates (82.2%) compared with those with more than a high school education (66.6%). Differences were statistically significant in multivariate models that included age, race/ethnicity, education, insurance, Medicaid coverage, and pregnancy intention. March of Dimes surveys[42,108,109] and the California Health Information Survey[112] also found that folic acid supplement consumption increases with education.

Differences by Income

Studies consistently found that supplemental folic acid use increases with income. The National Birth Defects Prevention Study found rates of compliant folic acid supplement use as follows: 10.07 percent for households making less than $10,000; 26.05 percent for households making $10,000 to $50,000; 55.21 percent for households making more than $50,000.[105] Rhode Island PRAMS (2004 to 2008) found a similar pattern: Multivitamin use prior to pregnancy was 21.1 percent for households making less than $25,000, 30.2 percent for households making $25,000 to less than $50,000; 50.5 percent for households making $50,000 or more; $p<0.0001$).[107] March of Dimes surveys,[108,109] NHANES,[42] and other surveys[112] also found that folic acid supplement consumption increases with household income.

Differences by Insurance Status

State-level analyses of PRAMS data found differences in supplemental folic acid use by insurance status. Rhode Island PRAMS (2004 to 2008) found significant differences in folic acid supplement use prior to pregnancy as follows: 17.3 percent among women with no insurance, 25.5 percent among women with public insurance, and 44 percent among women with private insurance ($p<0.0001$).[107] Texas PRAMS (2002 to 2010) found no daily multivitamin use was higher among women without health care coverage before pregnancy (83.2 percent) compared with those with coverage (67.9%) and among women on Medicaid (82.7%) compared with those not on Medicaid (64.7%). Differences were statistically significant in multivariate models that included age, race/ethnicity, education, insurance, Medicaid coverage, and pregnancy intention.[106]

Differences by Employment Status

The National Birth Defects Prevention Study found higher rates of compliant folic acid supplement use among women who were employed (35.47%) versus those who were unemployed (24.93%).[105]

Differences by Marital Status

Rhode Island PRAMS (2004 to 2008) found higher supplemental folic acid use prior to pregnancy among married women (44%) compared with nonmarried women (21.2%) ($p<0.0001$).[107]

Differences by Pregnancy Intention

State-level analyses of PRAMS data found that women intending pregnancy have higher rates of supplemental folic acid use than women not intending pregnancy. Rhode Island PRAMS (2004 to 2008) found significant differences in folic acid supplement use prior to pregnancy by pregnancy intention (44.5% among women intending pregnancy, 19.4% among women not intending pregnancy, $p<0.001$).[107] Texas PRAMS (2002 to 2010) found that no daily multivitamin use was more common among women not intending pregnancy (85.6%) than among those intending pregnancy (66.5%). Differences were statistically significant in multivariate models that included age, race/ethnicity, education, insurance, Medicaid coverage, and pregnancy intention.[106]

The National Birth Defects Prevention Study found higher rates of compliant folic acid supplement use among women not using birth control (33.51%)—who may be intending pregnancy—than among women using birth control (29.48%).[105]

Differences by U.S. Versus Foreign Born and Years in the United States

The National Birth Defects Prevention Study found higher rates of compliant folic acid supplement use among women born in the United States (35.94%) than among foreign-born women (18.5%). The 2008 March of Dimes survey of Spanish-language-dominant Hispanic women found rates of daily folic acid supplement used varied by number of years in the United States: less than 5 years in the United States (10%), 5 to 10 years in the United States (19%), 10+ years in the United States (24%), and born in the United States (18%).[109]

Differences by Parity

Rhode Island PRAMS (2004 to 2008) found differences in folic acid supplement use prior to pregnancy by parity: 37.1 percent first birth and 32.6 percent for second or higher birth ($p=0.0012$). NHANES 2003 to 2006 reports folic acid supplement use by parity: 32.4 percent for women with no live births, 30.3 percent for women with one live birth, and 31.3 percent for women with two or more live births.[42] The 2008 March of Dimes survey of Spanish-language-dominant Hispanic women found that daily folic acid supplement use was lowest among women who had never been pregnant (12%) compared with women who had been pregnant in the past 2 years or who were currently pregnant (20%), last pregnant 3 to 4 years ago (26%), or 5 or more years ago (23%).[109]

Differences by Health Behaviors/Health Status

The National Birth Defects Prevention Study found higher rates of compliant folic acid supplement use among nonsmokers (35.13%) versus smokers (21.93%) and among women among who had any alcohol intake in 3 months prior to conception (38.01%) compared with no alcohol intake (27.65%).[105] NHANES 2003 to 2006 found use of folic acid supplements was lower among women who have diabetes (17% vs. 32.1% among women who do not have diabetes).[42]

Effect of Folic Acid Supplementation Outside the Periconceptional Period on Neural Tube Defects

We did not find studies examining the effect of folic acid supplementation outside the periconceptional period on NTDs.

Variation in Effect of Folic Acid Supplementation by Medical Risk Factors

To date, the effect of folic acid supplementation on NTDs in pregnancies complicated by medical risk factors, including obesity, diabetes, seizure disorders, and folic acid antagonists (e.g., methotrexate), has been incompletely investigated, leaving physicians and their patients with limited guidance on dosage or interval of dosing in important subgroups of women. We sought to determine the available evidence on the effect of periconceptional folic acid supplementation in certain high-risk, yet moderately prevalent subgroups of pregnant women. Published studies do not provide direct evidence for developing clinical guidelines but do provide insight on the current state of knowledge of the effects of folic acid supplement in women with medical risk factors and identify important gaps and research needs. Although the findings from several large population-based case-control studies are available for review, there are relatively few cases of NTDs. Also, there is potential recall bias because folic acid supplementation is assessed primarily by maternal interviews or questionnaires completed 6 months or more after infant delivery.

Diabetes

Offspring of women with pregestational diabetes have a two- to fourfold increased risk of a wide range of birth defects. Prior studies in humans and animal models show that glucose control is an important prevention method. Additionally studies suggest that micronutrient levels, including folic acid, may play a key role in the pathogenesis of NTDs and other birth defects. Larger epidemiologic studies in this area have focused primarily on the joint effects of diabetes and obesity and folic acid intake to better determine the association of folic acid supplementation across key groups: no diabetes or obesity and folic acid use (reference group), no diabetes or obesity and no folic acid intake, diabetes and/or obesity and folic acid use, diabetes and/or obesity and no folic acid use (highest risk group). In one of the largest population-based studies, the Birth Defects Prevention Study (1997 to 2004)[113,114] identified 14,721 cases (infants with cardiac or noncardiac birth defects, including spina bifida and anencephaly) and 5,437 control infants and assessed the joint effects of maternal diabetes and folic acid consumption on birth defect development. Periconceptional folic acid supplementation was defined as intake in the month before conception or during the first 3 months of pregnancy. Women with pregestational

diabetes and no use of folic acid supplementation had an increased odds of birth defects overall, but the findings for specific birth defects must be interpreted with caution because they are limited by a small number of cases. Regarding spina bifida, there was a nonsignificant twofold increase (odds ratio [OR], 2.37; 95% CI, 0.21 to 26.65) in the risk of spina bifida among women with diabetes and no folic acid supplementation compared with women without diabetes who were taking folic acid supplements (reference group). There was a higher odds of anencephaly in this same group (OR, 31.56; 95% CI, 4.98 to 199.94).

The Slone Epidemiology Birth Defects Study[115] assessed the effect of periconceptional folic acid supplementation on NTDs within the setting of diabetes and obesity. Folic acid intake was ascertained through maternal interviews conducted within 6 months of delivery and was operationalized for analysis as 400 µg/day or more versus less than 400 µg/day. Spina bifida was more likely to occur in women who had diabetes or obesity than in those without either condition (0.7% and 19% vs. 0.4% and 10.8%). In analyses stratified by folic acid use, pregnancies with diabetes and <400 µg/day of folic acid had a statistically significant odds of NTDs (adjusted OR [aOR], 3.95; 95% CI, 1.56 to 10.00). Among pregnancies with appropriate folic acid supplementation and diabetes, there was a lower, but statistically significant, odds of NTDs (aOR, 1.31; 95% CI, 0.7 to 10).

A smaller study[116] among pregnant women with diabetes (n=31) and without diabetes (n=54) found no difference in dietary, serum, or red blood cell folate concentrations between the two groups, after adjusting for the extent of folic acid supplementation. These findings suggest that there is no difference in folic acid metabolism among women with and without diabetes, but the findings will need to be confirmed in a larger study. Additionally, while the level of glycemic control in early pregnancy is hypothesized to influence development of cardiac defects, the role of glycemic control on the conversion of homocysteine to methionine, the pathway thought to be most important to the development of NTDs, is not known, and there was no adjustment for glucose levels or the degree of glucose control in the analysis. Finally, it may be that the NTDs among women with diabetes may occur through multiple pathways.

Maternal Obesity

The epidemic of maternal obesity in the United States has drawn attention to whether the recommended daily dose of periconceptional folic acid supplementations is sufficient for women with an elevated body mass index (BMI). It is unclear, however, whether lower concentrations of folate in overweight/obese pregnant women are associated with a higher risk of NTDs and, therefore, whether the effect of folic acid supplementation varies with obesity. Although there are no recommendations specifically for overweight or obese women in the United States, some countries have recommended higher dosages up to 5 mg daily for overweight women. Prior studies have reported an inverse association between BMI and concentrations of micronutrients, including folic acid. Lower folic acid levels have been documented with increasing BMI, although a direct effect on the incidence of NTDs has not been observed. In one study,[117] serum folate concentrations and dietary intake of folate was assessed across BMI quartiles at mid- and late pregnancy among 802 and 660 women, respectively. A statistically significant association between BMI and folate concentrations was reported at mid-pregnancy (p for trend=0.001). While these data suggest a decrease in folic acid levels during pregnancy, the time frame is mid- to late pregnancy, which is well beyond the first 28 days of gestation in which maternal folate concentrations prevent NTDs.

Folic Acid Antagonists and Seizure Medications

We did not find conclusive evidence that the effect of folic acid supplementation on prevention of NTDs varies with the use of folic acid antagonists or seizure medications. Jentink and colleagues[118] conducted a registry-based case-control study of infants with spina bifida (cases) to infants with other congenital malformations unrelated to folic acid metabolism (controls) to determine the effect of periconceptional folic acid supplementation (4 weeks prior to conception through the first 8 weeks of pregnancy) on the risk of NTDs among women with epilepsy and treatment with valproic acid or carbamazepine. Over the study time period, 11,864 pregnancies with congenital malformations (197 pregnancies with spina bifida) were identified. Sixty-six women were exposed to anti-epileptic drugs. There was no statistically significant effect of folic acid supplementation on pregnancy outcomes in women exposed to valproic acid or carbamazepine (OR, 0.9; 95% CI, 0.2 to 4.3). In a subsequent analysis, Jentenk[119] examined the effect of folic acid supplementation on NTDs in pregnancies exposed and unexposed to valproic acid alone. Among pregnancies unexposed to valproic acid, there was a 50 percent reduction in NTDs with folic acid supplementation (OR, 0.5; 95% CI, 0.3 to 0.7). Among pregnancies exposed to valproic acid, there was no effect of folic acid supplementation on the incidence of NTDs (OR, 1.0; 95% CI, 0.1 to 7.6). There is little evidence to suggest that folic acid has a diminished protective effect on NTDs in women on anti-epileptic drugs and essentially no data on the effect of various dosages of folic acid supplementation on NTDs. First trimester exposure to valproic acid is associated with a 1 to 2 percent risk of NTDs, but the mechanism by which NTDs occur in the setting of valproic acid exposure is unclear, and further investigations are needed to better understand the biological pathways in which valproic acid may affect neural tube closure.

Several folic acid antagonists were evaluated in a large case-control study by Hernandez-Diaz.[88] Reported findings indicate a higher likelihood of NTDs (OR, 2.8; 95% CI, 1.7 to 4.6) with exposure to any one of several folic acid antagonists (including carbamazepine, phenobarbital, phenytoin, primidone, sulfasalazine, triamterene, and trimethoprim) in the first or second month of pregnancy compared with no exposure, even after adjusting for maternal characteristics, reproductive history, and folic acid supplementation. Subgroup analyses show a higher likelihood of NTDs with exposure to carbamzepine (6.9; 95% CI, 1.9 to 25.7) for carbamazepine or trimethoprim (4.8; 95% CI, 1.5 to 16.1). These findings should be interpreted with caution because the number of cases identified, particularly in subgroup analyses, was small. No studies were identified that evaluated the impact of folic acid supplementation in the setting of methotrexate, a folic acid antagonist used in the treatment of ectopic (i.e., tubal pregnancy) pregnancy.

Prior Neural Tube Defects

Meta-analysis findings[120] indicated that periconceptional folic acid supplementation was effective in reducing the risk of recurrent NTDs in the included studies of women with prior pregnancies complicated by NTDs. Evidence from three studies[121-123] (n=1,650 total pregnancies) of folic acid (doses ranging from 360 µg/day[95,121] to 4mg/day[122,123]) with a multivitamin (10/817 cases) compared with multivitamin alone or iron and calcium alone (32/833 cases) indicated a 67 percent reduction in NTDs (RR, 0.33; 95% CI, 0.17 to 0.66). (400 µg/day) with a multivitamin (10/817 cases) compared with multivitamin alone (32/833 cases) indicated a 67 percent reduction in NTDs (RR, 0.33; 95% CI, 0.17 to 0.66). Heterogeneity of the

pooled analysis was low (Chi^2, 1.25; I^2, 0.0%, p=0.74). The pooled relative risk was largely driven by the Medical Research Council Study, which had a total of 27/1,195 cases. Individual relative risk estimates, however, were consistent and statistically significantly associated with a reduction in the recurrence of NTDs across all three studies (0.29 to 0.42).

Other Fetal, Neonatal, or Maternal Benefits of Folic Acid Supplementation

Two Cochrane reviews evaluated the effect of folic acid supplementation on birth defects[124] and on maternal health and pregnancy outcomes.[125] Neither found other benefits of folic acid supplementation.

The Cochrane review on birth defects searched for evidence through July 2010. The review found no statistically significant effect of folic acid supplementation during the perinatal period when compared with no treatment, other micronutrients, or placebo on the prevention of congenital cardiovascular defects (three studies, N=2,869; RR, 0.55; 95% CI, 0.27 to 1.14), cleft palate (three studies, N=2,869; RR, 0.66; 95% CI, 0.11 to 3.92), cleft lip (three studies, N=2,869; RR, 1.00; 95% CI, 0.27 to 3.74), and other birth defects (excluding NTDs, cleft lip, cleft palate, and cardiovascular defects; average RR, 0.81; 95% CI, 0.38 to 1.77). The same review found no effect on miscarriage (five studies, N=7,618; RR, 1.10; 95% CI, 0.97 to 1.26), stillbirth (four studies, N=5,994; RR, 0.96; 95% CI, 0.51 to 1.83), or low birthweight (one study, N=186; RR, 0.80; 95% CI, 0.39 to 1.64).[124] In other analyses (restricted to placebo-controlled studies, expanded to include folic plus other micronutrients), the lack of effect persisted.

The Cochrane review on maternal health and pregnancy outcomes searched for evidence through December 2012.[125] The reviews found no effect of folic acid, when compared with no folic acid, on preterm birth (three studies, N=2,959; RR, 1.01; 95% CI, 0.73 to 1.38), stillbirths or neonatal deaths (three studies, N=3,110; RR, 1.33; 95% CI, 0.96 to 1.85), low birthweight (less than 2,500 g, three studies, N=3,089; RR, 0.80; 95% CI, 0.63 to 1.02), or predelivery anemia (eight studies, N=4,149; RR, 0.62; 95% CI, 0.35 to 1.10).[125]

Limitations of the Review

The limitations of this review arise from scoping decisions and the limitations of the evidence. As with the previous review, we restricted interventions to folic acid supplementation and did not consider food fortification, counseling to increase dietary intake, or screening for NTDs. The review did not examine the benefits of folic acid supplementation on benefits other than averted NTDs systematically, although we considered this issue as a contextual question. Finally, we did not evaluate systematically the effect of folic acid supplementation among high-risk populations such as women with previous pregnancies with NTDs; we considered this issue as contextual question.

Limitations of the evidence relate to insufficient data and the quality of evidence as a whole. We found 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 use of RCTs for this question. Observational studies carry limitations of case ascertainment and recall bias, and these two sources of bias serve to reduce the observed effect of folic acid supplements on NTDs.

Future Research Needs

The results showing lack of benefit from folic acid supplementation of more recent studies (case-control studies) run counter to the relatively consistent older studies that show benefit (trial, cohort studies, and case-control studies). This difference can potentially be attributed to a real attenuation of the effect of folic acid supplementation in the context of food fortification, or it can be attributed to design issues. Future research attempting to separate design effects from the real effects of the intervention need to consider important study design constraints.

Given ethical considerations about withholding folic acid from pregnant women, no trials of folic acid supplementation versus placebo are likely in the future. Additional case-control studies will likely encounter very similar issues of recall bias. Prospective studies could potentially shed light on the real effect of the intervention, provided they collect complete dietary and supplemental intake using consistent measurement tools and ensure good case ascertainment. Medication event monitoring systems (pill bottles fitted with a tracking device that records the date and times the container is opened and closed) could potentially improve the validity of adherence. Prospective studies that have access to state-based registries of birth defects may be able to ensure a higher rate of case ascertainment. Prospective studies by definition, however, will not be entirely representative of the primary care population because they will recruit women intending to get pregnant. Studies have shown that over half of the births in the United States were unplanned and that the rate of unintended pregnancy is higher among younger women than older women of childbearing age.[126]

Future research may have to rely on the intermediate links between folic acid intake, RBC folate concentrations, and outcomes in place of studies evaluating the direct link between intake and outcomes. As discussed earlier in this report, current studies of the effects of folic acid supplementation are limited by the inability to fully measure a woman's total consumption of folate (natural intake and supplementation). Studies that prospectively assess and quantify dietary intake, including the intake of foods fortified with folic acid and folic acid supplementation, and RBCs can provide further evidence on the first part of this intermediate evidence chain. Retrospective or prospective studies that link RBCs and outcomes can provide further evidence on the second part of the intermediate evidence chain.

These findings can provide additional data to inform public health messaging about folic acid supplementation regimens that, with compliance, can achieve optimal concentrations of folate in the periconception period. As assays are standardized, future studies may be able to measure folate status more efficiently through plasma, serum, or RBC concentrations. RBC folate concentrations may offer a sufficiently consistent and precise measure of maternal levels and ensure maximal benefit in the reduction of NTDs. Further studies are needed to evaluate the effect of measuring this biomarker on NTD reduction and the ability to integrate RBC folate concentrations into population-based health policies.

Another potential research direction is to use simulation studies to discern the magnitude of effect of food fortification versus folic acid supplementation using older studies with fewer design flaws. Two ongoing trials (Appendix G) of high versus low dose (4 mg per day vs. 0.4 mg per day) in Netherlands and Italy, expected to be completed in 2016, can provide additional relevant information.

Future updates of this systematic review should evaluate the intermediate links between folic acid supplementation and other sources of folate intake, folate status, and outcomes.

In addition to unanswered questions of overall effectiveness, future research should evaluate differences in subpopulations. We found limited information on the extent to which folic acid

supplementation had a protective effect among Hispanic women and possible reasons for differences in subgroups.

Conclusion

Older studies with fewer design flaws, conducted before food fortification, show that folic acid supplementation provides protection against NTDs. Newer studies, conducted after food fortification with folate in the United States, do not demonstrate this protective effect. These studies, however, have the potential for misclassification and recall bias, both of which can serve to attenuate the effect of folic acid supplementation on NTDs. Although mandatory food fortification in the United States has been accompanied by a decline in NTD prevalence, variations in intake continue to leave over a quarter of the U.S. population with suboptimal RBC folate concentrations, suggesting a continued important role for folic acid supplement use.

Inconsistent results of effectiveness of NTDs among Hispanic women when compared with white or black women could be due to chance. We found no evidence of a dose-response effect, but studies had small numbers of cases for subanalyses. We did not find consistent evidence on timing of folic acid supplementation for benefits. We did not find consistent evidence of harms, specifically twinning, respiratory outcomes, and other harms (e.g., gastrointestinal symptoms, weight gain or loss). Limited evidence suggests that the association of folic acid supplementation with twinning is attenuated after adjustment for covariates.

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Table 1. Measures and Definitions

Measure	Definition
Recommended Daily Allowance (RDA)[127]	• The RDA is the average daily dietary nutrient intake level sufficient to meet the nutrient requirement of nearly all (97 to 98%) healthy individuals in a particular life stage and gender group. • If the standard deviation is available and the data are normally distributed, the RDA = estimated average requirement (EAR) + 2 SD of EAR. If data about variability in requirements are insufficient to calculate an SD, a coefficient of variation for the EAR of 10% is assumed. The resulting equation for the RDA is then RDA = 1.2 × EAR. • The RDA for folate is set by assuming a coefficient of variation of 10% because information is not available on the standard deviation of the requirement for folate; the RDA is defined as equal to the EAR plus twice the CV to cover the needs of 97 to 98% of the individuals in the group. For folate the RDA is 120% of the EAR. • The RDA for both men and women is 400 µg/day of dietary folate equivalents.
Dietary Folic Equivalent (DFE)	• 1 DFE: 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach[71]
Estimated Average Requirement (EAR)	• The EAR is the average daily nutrient intake level estimated to meet the requirement of half the healthy individuals in a particular life stage and gender group. • EAR for females 15–50: 320 DFE[71] • The 320 DFE is based on 1 study of 5 patients who were fed a diet of 319 DFE.[128] Of these women, 3 had RBC folate <305 nmol/L, suggesting that with 320 DFE half would have RBC folate over 305 nmol/L. • The threshold of 305 nmol/L (140 ng/mL) of folate was chosen as the cutoff point for adequate folate status based on evidence that lower levels were associated with the appearance of hypersegmented neutrophils (1 case[129]; 2 cases[130] and its association with megaloblastic anema (40 patients with megaloblastic anemia also had RBC folate <305 nmol/L[131]; 238 pregnant women with RBC <327 nmol/L had megoblastic marrow[132] or chromosomal damage (8 patients with RBC folate <305 nmol/L had a threefold higher frequency of cellular micronuclei (suggesting DNA and chromosomal damage) than 14 control patients
Plasma/serum folate concentration	• Reflects current concentrations of folate in the circulation based on intake of folate that occurs naturally in food, fortified foods with folic acid and folic acid supplementation. • Because plasma/serum levels represent recent folate intake, it is not possible to differentiate between whether the result indicates a transient decline in folate intake or chronic deficiency. • No threshold value for plasma/serum folate concentration to prevent NTDs. Further research is necessary to correlate plasma/serum levels with RBC folate concentrations.
Red Blood Cell (RBC) Folate Concentrations	• Reflects body stores of folate; therefore, considered to be more accurate of folate status than plasma or serum folate concentrations. • RBC folate levels can be assessed with microbiological assays or commercial protein-binding assays on automated clinical analyzers. • At the population level, RBC folate concentrations should be above 400 ng/mL (906 nmol/L).[36] RBC is preferred over blood serum concentrations because there is less variation. • It is unknown how much natural food folate or folic acid intake is necessary to achieve adequate RBC folate concentrations.[36,37]

CV = coefficient of variation; DNA = deoxyribonucleic acid; nmol/L = nanomole/liter: NTD = neural tube defect; SD = standard deviation; µg = micrograms.

Table 2. Current guidelines for folic acid supplementation

Organization	Definition of Treatment Population	Guideline
American College of Obstetrics and Gynecology[65]	General population: Women capable of becoming pregnant	Folic acid supplementation of 400 µg per day is recommended during the periconceptional period to reduce the occurrence and recurrence of NTDs in low-risk women.
	High-risk population: Women at high risk of NTDs or who have had a previous pregnancy with an NTD	Folic acid supplementation of 4 mg per day is recommended for women at high risk of NTDs.
American Academy of Pediatrics[66]	General population: Women with no history of a previous pregnancy affected by an NTD	All women of childbearing age, capable of becoming pregnant, and having no history of a previous pregnancy affected by an NTD should consume 400 µg (0.4 mg) of folic acid.
	High-risk population: Women with a previous pregnancy affected by an NTD, having a close relative with an NTD, having diabetes, receiving treatment of valproic acid or carbamazepine for a seizure disorder, and having an NTD, or having a partner with an NTD	Women with a previous pregnancy affected by an NTD should consume 4,000 µg (4 mg) of folic acid per day starting 1 month before the time they plan to become pregnant and throughout the first 3 months of pregnancy, unless contraindicated. Women should be advised not to attempt to achieve the 4,000 µg daily dosage of folic acid by taking over-the-counter or prescription multivitamins containing folic acid because of the possibility of ingesting harmful levels of other vitamins. Women of other high-risk groups who are planning a pregnancy should discuss with their physician the advantages and disadvantages of increasing their daily periconceptional folic acid intake to 4,000 µg.
Public Health Service[67]	General population: Women of childbearing age in the United States	Women of childbearing age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid per day to reduce the risk of having a pregnancy affected with spina bifida or other NTDs. Because the effects of high intakes are not well known but include complicating the diagnosis of vitamin B12 deficiency, care should be taken to keep total folate consumption at less than 1 mg per day, except under the supervision of a physician.
	High-risk population: Women who have had a previous pregnancy affected by an NTD	Women who have had a previous pregnancy affected by an NTD should consult their physicians for advice when planning to become pregnant.
American Academy of Family Physicians[68]	Women planning or capable of pregnancy	Daily supplement containing 0.43 to 0.8 mg (400 to 800 µg) of folic acid is recommended for women planning a pregnancy or capable of pregnancy.
American Academy of Neurology[70]	Women with epilepsy	Folic acid supplementation should be instituted in women with epilepsy: no less than 0.4 mg/day and continued throughout pregnancy.
Institute of Medicine[71]	Women capable of becoming pregnant	400 µg of folic acid daily from fortified foods, supplements, or both in addition to consuming food folate from a varied diet

Table 2. Current guidelines for folic acid supplementation (continued)

Organization	Definition of Treatment Population	Guideline
National Institute for Health and Care Excellence[69]	General population: Women who may become pregnant and women in early pregnancy	A daily dose of 400 µg of folic acid before pregnancy and throughout the first 12 weeks is recommended.
	High-risk population: • Women or their partners have an NTD • Women who have had a previous baby with an NTD • Women or their partners who have a family history of NTDs • Women who have diabetes	A daily dose of 5 mg of folic acid is recommended for women at high risk who are planning a pregnancy or are in the early stages of pregnancy.

mg = milligram; NTD = neural tube defect; µg = microgram.

Table 3. Study characteristics of studies on the effect of folic acid supplementation on neural tube defects

Author Study Name Design Risk of Bias	Population	Intervention	Timing Setting
Czeizel et al., 1992[81] Czeizel et al., 1993[82] Czeizel et al., 1994[83] Czeizel et al., 1994[84] Czeizel et al., 1993[85] Czeizel et al., 1996[87] Czeizel et al., 1998[86] Hungarian RCT RCT Medium (fair quality)	Women planning a pregnancy without any delayed conception or infertility and not currently pregnant	G1: Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements)[86] (n=2,793) G2: Trace-element supplement (copper, manganese, zinc, low dose of vitamin C)[87] (n=2,660)	28 days before conception and at least until the date of the second missed menstrual period.[84] HPS began 3 months before a pregnancy is planned and continues for the first 3 months after conception. HPS provided information and counseling, examinations, and interventions during all trimesters by qualified nurses.
Czeizel et al., 2004[74] Hungarian Cohort Cohort Medium (fair quality)	Women planning a pregnancy without any delayed conception or infertility and not currently pregnant	G1: Women supplemented with multivitamin (n=3,056) G2: Nonsupplemented women (n=3,056)	Before conception and at least until first missed menstrual period. Supplemented cohort was recruited from the HPS. HPS provides information and counseling, examinations, and interventions during all trimesters by qualified nurses. Unsupplemented cohort was recruited during their first visit at an antenatal care clinic.
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	Women undergoing MSAFP screen or an amniocentesis	G1: Use of multivitamins containing folic acid G2: No use of multivitamins containing folic acid (or use less than 1 a week) Total: (n=22,715, multivitamin use information available)	3 months prior to pregnancy through 1st 3 months of pregnancy. Women were identified and recruited when they had a MSAFP screen or an amniocentesis at 16 weeks of pregnancy between October 1984 and June 1987. Women were receiving prenatal care and routine MSAFP screening in the practices of over 100 participating obstetricians.
Agopian et al., 2013[9] National Birth Defects Prevention Study Case-control Medium (fair quality)	Mothers with and without pregnancies affected by birth defects	G1: Spina bifida or anencephaly live births, fetal deaths, and elective pregnancy terminations (n=1,239) G2: Live-born controls without major birth defects (n=8,494)	Folic acid supplementation before pregnancy through 1st month of pregnancy. Population-based surveillance systems in 10 states. Data collected from medical records, birth certificate data, or hospital birth logs.

Table 3. Study characteristics of studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Study Name Design Risk of Bias	Population	Intervention	Timing Setting
Mosley et al., 2008[80] National Birth Defects Prevention Study Case-control Medium (fair quality)	Mothers with and without pregnancies affected by birth defects	G1: Spina bifida or anencephaly live births, fetal deaths, and elective pregnancy terminations (n=565) G2: Live-born controls without major birth defects (n=3,691)	Folic acid supplementation before pregnancy through 1st month of pregnancy. Population-based surveillance systems in 10 states. Data collected from medical records, birth certificate data, or hospital birth logs.
Ahrens et al., 2011[11] Slone Birth Defects Study Case-control Medium (fair quality)	Mothers with and without pregnancies affected by birth defects	G1: Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation (n=205) G2: Live-born nonmalformed infants (n=6,357)	Folic acid supplementation 2 months before the last menstrual period and 1 month after last menstrual period. Cases identified from discharge records of participating hospitals serving the areas surrounding Boston, MA; Philadelphia, PA; San Diego, CA; and Toronto, Canada and through birth defect registries in Massachusetts and New York State. Nonmalformed controls selected each month from study hospitals' discharge lists or from statewide birth records.
Hernandez-Diaz et al., 2001[88] Slone Birth Defects Study Case-control Medium (fair quality)	Mothers of malformed children	G1: Cases with NTDs (spina bifida, anencephaly, and encephalocele, or other NTDs) (n=1,242) G2: Infants with malformations not related to vitamin supplementation (n=6,660)	Any time during the 2 months after the last menstrual period. Participants of the Slone Epidemiology Unit Birth Defects Study. Study interviewed mothers of malformed children born in the greater metropolitan areas of Boston, MA; Philadelphia, PA; Toronto, Canada; and between 1983 and 1985, part of the state of Iowa. Subjects identified through review of admissions and discharges at major referral hospitals and clinics and through regular contact with newborn nurseries in community hospitals. A random sample of nonmalformed infants was identified at the birth hospitals as potential controls (only after 1993).

Table 3. Study characteristics of studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Study Name Design Risk of Bias	Population	Intervention	Timing Setting
Werler et al., 1993[92] Case-control Slone Birth Defects Study Medium (fair quality)	Mothers with NTD-affected pregnancies and mothers with pregnancies affected by other major malformations	G1: Live-born, stillborn infants, and therapeutic abortions with anencephaly, spina bifida, or encephalocele (n=436) G2: Live-born, stillborn infants, and therapeutic abortions with other major malformations (n=2,615)	Periconceptional period (interval from 28 days before the LMP through the 28 days after the LMP) (the first lunar month). Study subjects recruited from tertiary and birth hospitals in greater metropolitan Boston, MA; Philadelphia, PA; and Toronto, Ontario. Primary physicians of potential subjects were asked for permission to contact mothers.
Suarez et al., 2000[20] Texas Department of Health's Neural Tube Defect Project Medium (fair quality)	Mothers with and without NTD-affected pregnancies	G1: Infants or fetuses who had anencephaly (including craniorachischisis and iniencephaly), spina bifida, or encephalocele identified at birth or prenatally (n=148) G2: Normal live births (n=158)	3 months before conception to 3 months after conception. Texas Department of Health's Neural Tube Defect Project, occurrence of NTDs in 14 Texas counties along the U.S.-Mexico border identified at birth or prenatally between January 1995 and February 1999. Surveillance included hospitals, birthing centers, genetics clinics, ultrasound centers, licensed abortion centers, and approximately 150 midwives in the region.
Shaw et al., 1995[75] California Birth Defects Monitoring Program Case-control Medium (fair quality)	Mothers with and without singleton pregnancies affected by reportable birth defects	G1: Singleton live-born infants and electively terminated fetuses with an NTD (anencephaly, spina bifida cystic, craniorhachischisis, and iniencephaly) (n=538) G2: Singleton live births without a reportable birth defect (n=539)	3 months before pregnancy and/or first 3 months after conception. CBDMP, birth years between June 1, 1989, and May 31, 1991. Cases were women who had live-born and stillborn infants with NTDs and those who had NTD-affected pregnancies that were terminated after prenatal diagnosis (February 1, 1989–January 31, 1991). Controls were an equal number of singleton live births randomly selected in proportion to hospital's contributions to total population of infants born alive in CA.

Table 3. Study characteristics of studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Study Name Design Risk of Bias	Population	Intervention	Timing Setting
Mills et al., 1989[89] National Institute of Child Health and Human Development Neural Tube Defects Study (data from California and Illinois) Case-control Medium (fair quality)	Mothers with and without pregnancies affected by birth defects	G1: Cases, mothers of an infant or fetus with an NTD (n= 571) G2: Controls, mothers of normal infants (n=573) G3: Controls, mothers of an abnormal or stillborn infant or fetus (n=546)	Vitamin use 30 days before the first day of LMP and ending approximately 45 days thereafter. Study based in CA and IL. Cases included mothers of an infant or fetus with an NTD diagnosis prenatally or postnatally between June 15, 1985, and April 30, 1987, in IL or between August 1, 1985, and April 30, 1987, in CA.

CA = California; CBDMP = California Birth Defects Monitoring Program; G = group; HPS = Hungarian Preconceptional Service; IL = Illinois; LMP = last menstrual period; MA = Massachusetts; MSAFP = maternal serum a-fetoprotein; n = number; NTD = neural tube defect; PA = Pennsylvania; RCT = randomized controlled trial.

Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects

First Author, Year Design Risk of Bias	Interventions	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Czeizel et al., 1992[81] Czeizel et al., 1993[82] Czeizel et al., 1994[83] Czeizel et al., 1994[84] Czeizel et al., 1993[85] Czeizel et al., 1996[87] Czeizel et al., 1998[86] RCT Medium (fair quality)	Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements) Trace element supplement (copper, manganese, zinc, low dose of vitamin C)	Prospective, confirmed by (1) asking women; (2) checking women's record of supplement use, recorded daily with basal body temperatures; and (3) checking boxes of supplements for unused tablets	Live births, termination in the second trimester following prenatal diagnosis, and stillbirths with NTD	Live births, terminations in the second trimester following prenatal diagnosis, and stillbirths without NTD	1984–1992	(Peto) 0.131 (0.026–0.648)	Cases in exposed arm: 0 Cases in control arm: 6 N in exposed arm: 2,471 N in control arm: 2,391	None

Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects (continued)

First Author, Year Design Risk of Bias	Interventions	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Czeizel et al., 2004[74] Cohort Medium (fair quality)	Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements) No supplement	Prospective, confirmed by (1) asking women; (2) checking women's record of supplement use, recorded daily with basal body temperatures; and (3) checking boxes of supplements for unused tablets	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 >1,000 gm) with NTD	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 >1,000 gm) without NTD	1993–1996	0.11 (0.01–0.91)	Cases in exposed arm: 0 Cases in control arm: 9 N in exposed arm: 3,056 N in control arm: 3,056	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

Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects (continued)

First Author, Year Design Risk of Bias	Interventions	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	Multivitamins containing folic acid weeks 1–6 No multivitamins or multivitamins not containing folic acid	Interviewed at the time that the laboratory received the alphafetoprotein or amniocentesis test (15–20 weeks of pregnancy)	NTD, defined as spina bifida, anencephaly, or encephalocele alone or in combination with other defects from pregnancy outcome data ascertained through questionnaires to delivering physician or mothers (for nonresponsive physician)	No NTD	1984–1987	0.27 (0.12–0.59)	Cases in exposed arm: 10 Cases in control arm: 11 N in exposed arm: 10,713 N in control arm: 3,157	None

Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects (continued)

First Author, Year Design Risk of Bias	Interventions	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	Multivitamins containing folic acid weeks 7 and beyond No multivitamins or multivitamins not containing folic acid weeks and onward	Interviewed at the time that the laboratory received the alphafetoprotein or amniocentesis test (15–20 weeks of pregnancy)	NTD, defined as spina bifida, anencephaly, or encephalocele alone or in combination with other defects from pregnancy outcome data ascertained through questionnaires to delivering physician or mothers (for nonresponsive physician)	No NTD	1984–1987	0.92 (0.45–1.87)	Cases in exposed arm: 25 Cases in control arm: 11 N in exposed arm: 7,795 N in control arm: 3,157	None

Table 4. Results of prospective studies on the effect of folic acid supplementation on neural tube defects (continued)

First Author, Year Design Risk of Bias	Interventions	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	Multivitamins containing folic acid weeks 7 and beyond No multivitamins or multivitamins not containing folic acid weeks and onward	Interviewed at the time that the laboratory received the alphafetoprotein or amniocentesis test (15–20 weeks of pregnancy)	NTD, defined as spina bifida, anencephaly, or encephalocele alone or in combination with other defects from pregnancy outcome data ascertained through questionnaires to delivering physician or mothers (for nonresponsive physician)	No NTD	1984–1987	0.92 (0.45–1.87)	Cases in exposed arm: 25 Cases in control arm: 11 N in exposed arm: 7,795 N in control arm: 3,157	None

CI = confidence interval; gm = grams; N = number; NTD = neural tube defect

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Agopian et al., 2013[9,133] Case-control Medium (fair quality)	Any folic acid supplementation (folic acid, multivitamin, or prenatal supplement) during the month before pregnancy and the first month of pregnancy No supplementation during the month before pregnancy and the first month of pregnancy	Interviews are targeted for completion within 6 months of the expected date of delivery but must be completed no earlier than 6 weeks and no later than 24 months after the expected date of delivery.	Spina bifida or anencephaly live births, fetal deaths, and elective pregnancy terminations	Live-born controls without major birth defects	1997–2007	0.93 (0.82–1.06)	Cases:1239 N exposed:617 N not exposed:619 Controls: 8494 N exposed:4293 N not exposed:4167	Body mass index ≥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
Mosley et al., 2008[80] Case-control Medium (fair quality)	Consistent use (taking supplements at least half the number of days, ≥60 days, from 3 months before pregnancy to the first month of pregnancy) No supplementation during the month before pregnancy and the first month of pregnancy	Interviews are targeted for completion within 6 months of the EDD but must be completed no earlier than 6 weeks and no later than 24 months after the expected date of delivery.	Anencephaly live births, fetal deaths, and elective pregnancy terminations	Live-born controls without major birth defects	1998–2003	1.2 (0.8–1.9)	Cases: 180 N exposed: 38 N not exposed:81 Controls:3691 N exposed:965 N not exposedl:1,778	Maternal race and education

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Mosley et al., 2008[80] Case-control Medium (fair quality)	Consistent use (taking supplements at least half the number of days, ≥60 days, from 3 months before pregnancy to the first month of pregnancy) No supplemen-tation during the month before pregnancy and the first month of pregnancy	Interviews are targeted for completion within 6 months of the EDD but must be completed no earlier than 6 weeks and no later than 24 months of the EDD.[134]	Spina bifida live births, fetal deaths, and elective pregnancy terminations	Live-born controls without major birth defects	1998–2003	1.4 (1.0–1.8)	Cases: 385 N exposed: 97 N not exposed:188 Controls:3691 N exposed:965 N not exposed:1,778	Maternal race, BMI, and pregnancy
Mosley et al., 2008[80] Case-control Medium (fair quality)	Initiating supplement use in the first month of pregnancy No supplementation during the month before pregnancy and the first month of pregnancy	Interviews are targeted for completion within 6 months of the EDD but must be completed no earlier than 6 weeks and no later than 24 months of the EDD.	Anencephaly live births, fetal deaths, and elective pregnancy terminations	Live-born controls without major birth defects	1998–2003	1.7 (1.2–2.4)	Cases: 180 N exposed:61 N not exposed:81 Controls:3691 N exposed:948 N not exposed:1,778	Maternal race and education

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Mosley et al., 2008[80] Case-control Medium (fair quality)	Initiating supplement use in the first month of pregnancy No supplementation during the month before pregnancy and the first month of pregnancy	Interviews are targeted for completion within 6 months of the EDD but must be completed no earlier than 6 weeks and no later than 24 months of the EDD.[134]	Spina bifida live births, fetal deaths, and elective pregnancy terminations	Live-born controls without major birth defects	1998–2003	1.1 (0.9–1.5)	Cases: 385 N exposed: 100 N not exposed:188 Controls:3691 N exposed:948 N not exposed:1,778	Maternal race, BMI, and pregnancy
Ahrens et al., 2011[11] Case-control Medium (fair quality)	Consistent users of prenatal vitamins, multivitamins, and folic acid supplements (≥4 days per week at least 2 of 3 periconceptional months) No folic acid supplementation, use (<1 day per month, or use only during LM -2)	Interviews conducted within 6 months of delivery	Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation	Live-born nonmalformed infants	1998–2008	1.11 (0.74–1.65)	Cases: 205 N exposed: 83 N not exposed: 59 Controls: : 6357 N exposed: 2573 N not exposed: 1438	Race, BMI, pregnancy intent, and study center

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Ahrens et al., 2011[11] Case-control Medium (fair quality)	Early pregnancy initiators of prenatal vitamins, multivitamins, and folic acid supplements (≥4 days per beginning in first or second postconcep-tional months No folic acid supplementa-tion, use (<1 day per month, or use only in LM -2)	Interviews conducted within 6 months of delivery	Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation	Live-born nonmalformed infants	1998–2008	0.79 (0.54–1.16)	Cases: 205 N in exposed: 60 N not exposed: 59 Controls: 6357 N exposed: 2293 N not exposed: 1438	Race, BMI, pregnancy intent, and study center
Ahrens et al., 2011[11] Case-control Medium (fair quality)	Inconsistent users of prenatal vitamins, multivitamins, and folic acid supplements use patterns not defined as consistent, early pregnancy or nonuse No folic acid supplementa-tion, use (<1 day per month, or use only during LM -2)	Interviews conducted within 6 months of delivery	Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation	Live-born nonmalformed infants	1998–2008	2.20 (0.64–7.62)	Cases: 205 N in exposed: 3 N not exposed: 59 Controls: 6357 N exposed: 53 N not exposed:1438	Race, BMI, pregnancy intent, and study center

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Hernandez-Diaz et al., 2001[88] Case-control Medium (fair quality)	Folic acid during the 2 months after the last menstrual period No folic acid use	Interviews conducted within 6 months of delivery	Live-born and stillborn infants and therapeutic abortuses with NTD (anencephaly, spina bifida, encephalocele, or other NTD); stillbirths and therapeutic abortions included from 1988 onward	Malformations other than NTDs	1976–1998	0.7 (0.5–0.8)	Cases: 1242 N exposed: 140 N not exposed: 715 Controls:6660 N exposed:939 N not exposed:3695	Interview year, region, maternal age, education, weight before pregnancy, and urinary tract infections or other infections early in pregnancy
Werler et al. 1993[92] Case-control Medium (fair quality)	Daily use in the periconceptional period (28 days before LMP through 28 days after LMP) No folic acid use	Interviews conducted within 6 months of delivery	Live-born and stillborn infants and therapeutic abortuses with NTD (anencephaly, spina bifida, or encephalocele)	Other major malformations	1988–1991	Relative risk: 0.6 (0.4–0.8)	Cases:436 N exposed: 34 N not exposed:250 Controls:2615 N exposed:339 N not exposed:1253	Maternal age, maternal education, annual family income, birth status
Suarez et al., 2000[20] Case-control Medium (fair quality)	Daily use in every month in the preconception period (≤ 3 months before conception) No folic acid use	Interviews were conducted approximately 1 month postpartum	Infants or fetuses who had anencephaly, spina bifida, or encephalocele identified at birth or prenatally	Control, normal live births	1995–1999	0.77 (0.19–3.22)	Cases:148 N exposed:3 N not exposed: 66 Controls:158 N exposed:4 N not exposed:68	None

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Suarez et al., 2000[20] Case-control Medium (fair quality)	Daily use in every month in the preconception period (≤ 3 months before conception) No folic acid use	Interviews were conducted approximately 1 month postpartum	Infants or fetuses who had anencephaly, spina bifida, or encephalocele identified at birth or prenatally	Control, normal live births	1995–1999	1.12 (0.22–5.78)	Cases:148 N exposed:3 N not exposed: 66 Controls:158 N exposed:4 N not exposed:68	Maternal age, education, obesity, and previous stillbirth or miscarriage
Suarez et al., 2000[20] Case-control Medium (fair quality)	Any use in every month in the preconception period (≤3 months before conception) No folic acid use	Interviews were conducted approximately 1 month postpartum	Infants or fetuses who had anencephaly, spina bifida, or encephalocele identified at birth or prenatally	Control, normal live births	1995–1999	1.12 (0.22–5.78)	Cases:148 N exposed:8 N not exposed: 66 Controls:158 N exposed:5 N not exposed:68	None
Suarez et al., 2000[20] Case-control Medium (fair quality)	Post conception period (≤ 3 months after conception) No folic acid use	Interviews were conducted approximately 1 month postpartum	Infants or fetuses who had anencephaly, spina bifida, or encephalocele identified at birth or prenatally	Control, normal live births	1995–1999	1.12 (0.22–5.78)	Cases:148 N exposed:74 N not exposed: 66 Controls:158 N exposed:85 N not exposed:68	None
Shaw et al., 1995[75] Case-control Medium (fair quality)	Vitamin supplements containing folic acid in the 3 months before conception No folic acid use	Interviews conducted an average of 5 months after delivery	Cases: Singleton live-born infants and electively terminated fetuses with an NTD (anencephaly, spina bifida cystic, craniorhach-ischisis, and iniencephaly)	Singleton live births without a reportable birth defect	1989–1991	0.65 (0.45–0.94)	Cases:538 N exposed:53 N not exposed: 207 Controls:539 N exposed:56 N not exposed:149	None

Table 5. Results of retrospective studies on the effect of folic acid supplementation on neural tube defects (continued)

Author Design Risk of Bias	Intervention Comparison	Timing of Measurement of Exposure	Outcome	Comparison	Period of Exposure	Odds Ratio (95% CI)	N	Adjustments
Shaw et al., 1995[75] Case-control Medium (fair quality)	Vitamin supplements containing folic acid in the 3 months after conception (assuming women who started in period before conception continued) No folic acid use	Interviews conducted an average of 5 months after delivery	Cases: Singleton live-born infants and electively terminated fetuses with an NTD (anencephaly, spina bifida cystic, craniorachischisis, and iniencephaly)	Singleton live births without a reportable birth defect	1989–1991	0.60 (0.46–0.79)	Cases:538 N exposed:37 N not exposed: 207 Controls:539 N exposed:27 N not exposed:149	None
Mills et al., 1989[89] Case-control Medium (fair quality)	Vitamin supplements containing folic acid (exposure defined taking supplements containing the RDA of at least 4 vitamins or a higher dose at least 6 days per week) None	Interviews were conducted no more than 3 months after delivery	NTDs, including anencephaly, meningocele, myelomengocele, encephalocelen, rachischisis, iniencephaly, and lipomeningocele	Controls, mothers of normal infants	1985–1987	1.00 (0.73–1.43)	Cases:565 N exposed:86 N not exposed: 464 Controls:567 N exposed:84 N not exposed:456	None

BMI = body mass index; CI = confidence interval; EDD = expected date of delivery; LM -2 = 2 months before last menstrual period; LMP = last menstrual period; N = number; NTD = neural tube defect.

Table 6. Variations in the effect of folic acid supplementation neural tube defects by race and ethnicity

Author Design Risk of Bias	Subgroup	N	Results
Ahrens et al., 2011[11] Case-control Medium (fair quality)	White, Non-Hispanic Black, non-Hispanic Hispanic	White, Non-Hispanic G1: 128 G2: 4535 Black, Non-Hispanic G1: 22 G2: 459 Hispanic G1: 39 G2: 892	White, Non-Hispanic Crude OR (95% CI) Consistent users: 0.78 (0.49–1.25) Early pregnancy initiators: 0.63 (0.38–1.06) Adjusted OR (95% CI) Consistent users: 0.93 (0.56–1.54) Early pregnancy initiators: 0.68 (0.40–1.16) Black, non-Hispanic Crude Odds Ratio (95% CI) Consistent users: 1.11 (0.34–3.61) Early pregnancy initiators: 0.77(0.29–2.02) Adjusted OR (95% CI) Consistent users: NC Early pregnancy initiators: 0.86(0.32–2.30) Hispanic Crude OR (95% CI) Consistent users: 1.81 (0.85–3.84) Early pregnancy initiators: 0.61 (0.27–1.38) Adjusted OR (95% CI) Consistent users: 2.20 (0.98–4.92) Early pregnancy initiators: 0.74 (0.32–1.70)

Table 6. Variations in the effect of folic acid supplementation neural tube defects by race and ethnicity (continued)

Author Design Risk of Bias	Subgroup	N	Results
Mosley et al., 2008[80] Case-control Medium (fair-quality)	White, black, Hispanic	Anencephaly White, non-Hispanic: 83 Black, non-Hispanic: 18 Hispanic: 67 Spina bifida White, non-Hispanic: 191 Black, non-Hispanic: 42 Hispanic: 134 Controls White, non-Hispanic: 2,173 Black, non-Hispanic: 431 Hispanic: 865	Anencephaly White, non-Hispanic Crude OR (95% CI) 3 months before pregnancy: 1.2 (0.7–2.1) First month of pregnancy: 1.5 (0.9–2.6) Black, non-Hispanic Crude OR (95% CI) 3 months before pregnancy: 2.8 (0.8–10.4) 1st month of pregnancy: 3.9 (1.3–11.5) Hispanic Crude OR (95% CI) 3 months before pregnancy: 0.7 (0.2–2.2) 1st month of pregnancy: 1.4 (0.8–2.5) Spina bifida White, non-Hispanic Crude OR (95% CI) 3 months before pregnancy: 1.3 (0.9–1.9) 1st month of pregnancy: 1.1 (0.8–1.7) Black, non-Hispanic Crude OR (95% CI) 3 months before pregnancy: 1.2 (0.5–2.8) 1st month of pregnancy: 0.6 (0.3–1.6) Hispanic Crude OR (95% CI) 3 months before pregnancy: 0.4 (0.2–1.2) 1st month of pregnancy: 1.3 (0.9–2.0)
Shaw et al., 1995[75] Case-control Medium (fair-quality)	Hispanic, Non-Hispanic White, Black, Other	Hispanic G1: 265 G2: 196 Non-Hispanic white G1: 217 G2: 272 Black G1: 27 G2: 31 Other G1: 28 G2: 39	OR for NTD from maternal use of a folic acid-containing vitamin in 3 months before conception (95% CI) Hispanic: 0.96 (0.44–2.10) Non-Hispanic: 0.62 (0.3 to -1.10) African American: 0.54 (0.09–3.20) Other: 4.3 (0.23–145) OR for NTD from maternal use of a folic acid-containing vitamin in first 3 months postconception OR (95% CI) Hispanic: 0.73 (0.49–1.10) Non-Hispanic: 0.58 (0.36–0.94) African American: 0.29 (0.08–1.10) Other: 1.9 (0.57–6.30)

CI = confidence interval; N = number; NC = North Carolina; = NTD = neural tube defect; OR = odds ratio.

Table 7. Variations in effect of folic acid supplementation on neural tube defects by dosage

Author Design Risk of Bias	Subgroup	N	Results
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	0, 1–399, 400–799, ≥800	0: 13,431 1–399: 2,489 400–799: 1,812 ≥800: 5,494	Relative risk of NTD (95% CI) dietary folate from supplements dietary folate equivalent/day (weeks 1–5) 1–399: 0.29 (0.07–1.2) 400–799: 0.41 (0.10–1.7) ≥800: 0.56 (0.24–1.3)
Shaw et al., 1995[75] Case-control Medium (fair-quality)	Any, <0.4, 0.4–0.9, ≥1.0	Use in 3 months before conception <0.4 G1: 53 G2: 56 0.4–0.9 G1: 29 G2: 32 ≥1.0 G1: 5 G2: 6 Use in 3 months before conception <0.4 G1: 37 G2: 27 0.4–0.9 G1: 243 G2: 322 ≥1.0 G1:42 G2:33 None G1: 207 G2: 149 Unknown G1: 4 G2: 2	OR for NTDs with maternal use of a folic acid-containing vitamin supplement in the 3 months before conception OR (95%) <0.4: 0.68 (0.43–1.10) 0.4–0.9: 0.65 (0.37–1.20) ≥1.0: 0.60 (0.16–2.30) OR for NTDs with maternal use of a folic acid- containing vitamin supplement 3 months after conception OR (95%) <0.4: 0.99 (0.56–1.80) 0.4–0.9: 0.54 (0.41–0.72) ≥1.0: 0.92 (0.54–1.60)

Table 7. Variations in effect of folic acid supplementation on neural tube defects by dosage (continued)

Author Design Risk of Bias	Subgroup	N	Results
Werler et al., 1993[92] Case-control Medium (fair quality)	≥1 mg, 0.5–0.9 mg, 0.4 mg, <0.4 mg	Daily dose G1: 34 G2: 339 Less than daily dose G1: 41 G2: 234 Relative risks according to daily folic acid dose among 18 case mothers (G1) and 322 control (G2) mothers who received periconceptional supplements and did not report knowledge of the hypothesis ≥1 mg G1: 3 G2: 52 0.5–0.9 mg G1: 2 G2: 15 0.4 mg G1: 8 G2: 185 <0.4 mg G1: 3 G2: 50	Calculated OR for daily vs. less than daily dose 0.57; 95% CI, 0.35–0.93 RR by dose among women who did not know hypothesis ≥1 mg folic acid dose in supplement RR (95% CI) (unclear if crude or multivariate): 0.4 (0.1–1.3) 0.5–0.9 mg folic acid dose in supplement RR (95% CI) (unclear if crude or multivariate): 0.9 (0.2–4.2) 0.4 mg folic acid dose in supplement RR (95% CI) (unclear if crude or multivariate): 0.3 (0.1–0.6) <0.4 mg folic acid dose in supplement RR (95% CI) (unclear if crude or multivariate): 0.5 (0.2–1.5)`
Mills et al., 1989[89] Case-control Medium (fair quality)	RDA or more vs. none Any amount vs. none	RDA or more G1: 86 G2: 70 G3: 84 Less than RDA G1: 15 G2: 17 G3: 27 None G1: 464 G2: 451 G3: 456	Calculated OR of RDA or more vs. less than RDA: 1.84; 95% CI, 0.92–3.71

CI = confidence interval; G = group; mg = milligrams; N = number; NTD = neural tube defect; RDA = recommended daily allowance; OR = odds ratio; RR = relative risk; vs. = versus.

Table 8. Variations in effect of folic acid supplementation on neural tube defects by timing

Author Design Risk of Bias	Subgroup	N	Results
Ahrens et al., 2011[11] Case-control Medium (fair quality)	Consistent users (4 or more days per week) 2 of 3 periconceptional months vs. initiating in the first month (4 or more days per week)	Spina bifida Consistent users G1: 83 G2: 2,573 Initiating in the first month G1:60 G2: 2,293	Calculated OR, 1.23, 95% CI, 0.88–1.73
Mosley et al., 2008[80] Case-control Medium (fair quality)	Consistent users 3 months before pregnancy through first month of pregnancy vs. initiating in the first month	Anencephaly Consistent users G1: 38 G2: 61 Initiating in the first month G1: 965 G2: 948	Anencephaly, calculated OR 0.61; 95% CI, 0.40–0.93
		Spina bifida Consistent users G1: 97 G2: 100 Initiating in the first month G1: 965 G2: 948	Spina bifida, calculated OR 0.95; 95% CI, 0.71–1.28
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort Medium (fair quality)	Women who did not use multivitamins after conception with women who used multivitamins in the first 6 weeks of pregnancy and women who started multivitamin use only after week 6	Use in weeks 1-6 G1:10 G2: 10,731 Use in weeks 7 and later G1: 25 G2: 7,795	Calculated OR, 0.29, 95% CI, 0.14–0.60
Suarez et al., 2000[20] Case-control Medium (fair quality)	Preconceptional use vs. postconceptional use	Preconceptional use G1:8 G2:5 Postconceptional use G1:74 G2:85	Calculated OR, 1.84; 95% CI, 0.58–5.86
Shaw et al., 1995[75] Case-control Medium (fair quality)	Use in 3 months before conception vs. use in 3 months before conception	Use in 3 months before conception Any G1: 88 G2:98 Use in 3 months before conception Any G1:322 G2:384	Calculated OR, 1.07; 95% CI, 0.77–1.48

CI = confidence interval; G = group; N = number; OR = odds ratio; vs. = versus.

Table 9. Harms of folic acid supplementation: Study characteristics of included twinning studies

Author Study Name Design Risk of Bias	Population	Intervention	Timing and Setting
Czeizel et al., 1992[81] Czeizel et al., 1993[82] Czeizel et al., 1994[83] Czeizel et al., 1994[84] Czeizel et al., 1993[85] Czeizel et al., 1996[87] Czeizel et al., 1998[86] Hungarian RCT RCT Medium (fair quality)	Women planning a pregnancy without any delayed conception or infertility and not currently pregnant	G1: Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements)[86] (n=2,793) G2: Trace-element supplement (copper, manganese, zinc, low dose of vitamin C)[87] (n=2,660)	28 days before conception and at least until the date of the second missed menstrual period[84] HPS began 3 months before a pregnancy is planned and continues for the first 3 months after conception. HPS provided information and counseling, examinations, and interventions during all trimesters by qualified nurses.
Vollset et al., 2005[76] Medical Birth Registry of Norway Cohort Medium (fair quality)	Women with singleton and twin pregnancies	G1: Preconceptional use of folate (n=11,077) G2: No preconceptional use of folate (n=164,965)	Preconception Medical Birth Registry of Norway, women who gave birth from December 1998 through the end of 2001. Information on IVF pregnancies obtained by contacting fertility clinics in Denmark and Sweden.

G = group; HPS = Hungarian Preconceptional Service; IVF = in vitro fertilization; n = number; RCT = randomized controlled trials.

Table 10. Harms of folic acid supplementation: Study characteristics of included asthma/wheezing studies

Author Study Name Design Risk of Bias	Population	Intervention	Timing and Setting
Yang, 2014[101] Meta- analysis Medium (fair quality)	Studies that examined folic acid exposure during the periconceptional period or during pregnancy and provided results on at least one allergic or respiratory outcome or outcome of interest	Folic acid supplementation	Supplementation during preconception and during pregnancy All available settings
Crider, 2013[94] Meta-analysis Low (high quality)	Studies that examined maternal folic acid supplementation during pregnancy on infant asthma	Folic acid supplementation	Supplementation during preconception and during pregnancy All available settings

Table 11. Results of prospective studies on the associations between folic acid supplementation and twinning

First Author, Design Risk of Bias	Intervention Groups (n)	Timing of Measurement Exposure	Outcomes	Relative Risk or Odds Ratio (95% CI)	N	Adjustments
Czeizel, 1994[84] Czeizel, 1996[87] RCT Medium (fair quality)	G1: Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements)[86] (n=2,793) G2: Trace-element supplement (copper, manganese, zinc, low dose of vitamin C)[87] (n=2,660)	28 days before conception and at least until the date of the second missed menstrual period[84]	Twinning	RR: 1.4 (0.97–2.25) RR: 1.6 (0.81–3.18)	Cases in exposed arm: 46 N in exposed arm: 2,421 Cases in control arm: 32 N in control arm: 2,345 Ovulation subgroup: Cases in exposed arm: 19 N in exposed arm: 141 Cases in control arm: 12 N in control arm: 143	None
Vollset et al., 2005[76] Cohort Medium (fair quality)	All pregnancies: G1: Preconceptional use of folate (N=11,077) G2: No preconceptional use of folate (N=164,965) Natural conception: G1: 10,457 G2: 164,965 IVF: G1: 620 G2: 2,000	Preconception	Twinning	OR: 1.59 (1.41–1.78) OR: 1.04 (0.91–1.18)	Cases in exposed arm: 329 N in exposed arm: 11,077 Cases in control arm: 2,825 N in control arm: 164,965 Cases in exposed arm: 175 N in exposed arm: 10,457 Cases in control arm: 2,282 N in control arm: 162,965 Cases in exposed arm: 154 N in exposed arm: 620 Cases in control arm: 543 N in control arm: 2,000	Maternal age and parity Maternal age, parity, and IVF

CI = confidence interval; G = group; IVF = in vitro fertilization; n = number; N = number; OR = odds ratio; RR = relative risk.

Table 12. Results of meta-analyses on the associations between folic acid supplementation and asthma/respiratory illness

First Author, Design Quality	Intervention Groups (n)	Timing of measurement Exposure	Outcomes	Relative Risk or Odds Ratio (95% CI)
Yang, 2014[101] Meta-analysis Fair quality	G1.Periconceptional use of folic acid (NR) G2: No use (NR)	Periconceptional period through pregnancy.	Child asthma	OR: 1.06, (0.99–1.14)
Crider, 2013[94] Meta-analysis Fair quality	G1. Periconceptional use of folic acid (NR) G2: No use (NR)	Periconceptional or first trimester	Asthma or wheezing. Other outcomes: atopy, eczema, and atopic dermatitis (includes LRTI, URTI, food reaction, sensitization)	Asthma: RR: 1.01 (0.78–1.30 Wheeze in infants/toddler; asthma in children: RR: 1.05 (1.02–1.09

CI = confidence interval; G = group; LRTI = lower respiratory tract infection; n = number; N = number; NR = not reported; OR = odds ratio; RR = relative risk; URTI = upper respiratory tract infections.

Table 13. Variation in harms of folic acid supplementation by timing

First Author, Design	Intervention Groups (n)	Timing of Measurement Exposure	Outcomes	Relative Risk or Odds Ratio (95% CI)
Crider, 2013[94] Systematic review	G1. Second or third trimester use of folic acid (NR) G2: No use (NR)	Second or third trimester	Asthma or Wheezing	Wheeze in infants/toddler RR: 1.20 (95% CI: 1.04–1.39) in 1 study[93] 14 other associations for asthma or wheezing not statistically significantly different[93,95]
			Other allergic outcomes	38 associations for other allergic outcomes not statistically

CI = confidence interval; G = group; NR = not reported; RR = relative risk

Table 14. Variation in harms of folic acid supplementation by dose

First Author, Design	Intervention Groups (n)	Timing of Measurement Exposure	Outcomes	Relative Risk or Odds Ratio (95% CI)
Crider, 2013[94] (citing Dunstan, 2012[102]) Systematic review	G1: >500 mg/day G2: 200-499 mg/day G3: <200 mg/day	Third trimester	Any allergic disease, sensitization, recurrent wheeze, eczema, food reactions, IgE-mediated food allergy, and sensitization to food allergens	12 associations overlap line of no difference. 2 span line of no difference for G3 vs. G1 (OR: 1.5; 95% CI, 1.0-2.5) and G2 vs. G1 (OR: 1.7; 95% CI, 1.0-2.8) for eczema.

CI = confidence interval; G = group; IgE = immunoglobulin E; mg = milligram; RR = relative risk; vs. = versus

Table 15. Summary of evidence for folic acid supplementation

Key Question	Number of Studies (Study Designs)	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ 1a: Extent to which folic acid supple-mentation reduces the risk for NTDs	12 (1 RCT, 2 cohort studies, 8 case-control studies,1 previous review)	**RCT (prefortification):** Peto odds ratio for NTDs: 0.131, 95% CI, 0.026–0.648, p=0.013 **Cohort studies (prefortification)**: Adjusted OR for NTDs: 0.11 (95% CI, 0.011–0.91); OR, 0.27 (95% CI, 0.12–0.59). **Case-control studies (prefortification):** Adjusted OR for NTDs: 0.7, 95% CI, 0.5–0.8; relative risk of for NTDs: 0.6, 95% CI, 0.4–0.8; OR for NTDs: 0.65 (95% CI, 0.45–0.94); (OR, 1.00, 95% CI, 0.73–1.40, p=0.97) **Case control studies (spanning pre- and postfortification):** adjusted OR for NTDs: 1.12, 95% CI, 0.22–5.78	Consistency: Generally consistent within the prefortification and postfortification eras, inconsistent over time Precision: Wide confidence intervals but clear indication of benefit in the prefortification era, narrower confidence intervals with confidence intervals 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 (prospective cohort studies) or recall bias (retrospective studies)	High for prefortification data; low for postfortifica-tion data	Generally applicable to primary care

Table 15. Summary of evidence for folic acid supplementation (continued)

Key Question	Number of Studies (Study Designs)	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
		Case control studies (postfortification): OR for NTDs: 1.11 (95% CI, 0.74–1.65) for consistent users; Adjusted OR for NTDs (anencephaly+spina bifida): 0.93, 95% CI, 0.82–1.06; Adjusted OR (anencephaly): 1.2, 95% CI, 0.8–1.9; Adjusted OR (spina bifida): 1.4, 95% CI, 1.0–1.8						
KQ 1b: Differences in effect of folic acid supplementation on NTDs by race/ ethnicity	3 (3 case-control studies)	No effect in one study; higher risk in second (adjusted OR for Hispanic women: 2.20, 95% CI, 0.98–4.92); less protective effect in third: risk reduction less marked for Hispanic women (OR, 0.96, 95% CI, 0.44–2.10) than non-Hispanic whites (OR, 0.62; 95% CI, 0.35–1.10) or blacks (OR, = 0.54; 95% CI, 0.0.09–3.20)	Inconsistent Imprecise	Undetected	Fair	Small numbers in each comparison, effects possibly due to chance	Low	Generally applicable to primary care

Table 15. Summary of evidence for folic acid supplementation (continued)

Key Question	Number of Studies (Study Designs)	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ 1c: Differences in effect of folic acid supplementation on NTDs by dosage, duration, and timing	Dosage: 4 (1 cohort study, 3 case-control studies) Duration: 0 Timing: 5 (1 cohort study, 4 case-control studies)	No indication of dose response in 3 of 4 studies. One study shows lower odds for daily use versus less than daily use (OR, .57; 95% CI, 0.35–0.93) Duration: none Timing: Older studies consistently show no effect of timing, 1 new study (postfortification) shows a protective effect of use before pregnancy on anencephaly but not spina bifida. The other new study did not find a protective effect for spina bifida.	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

Table 15. Summary of evidence for folic acid supplementation (continued)

Key Question	Number of Studies (Study Designs)	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ 2a: Harms associated with folic acid supplementation	Twinning in women: 2 (1 trial, 1 cohort)	The trial found no statistically significant differences in twin pregnancy rate (1.4; 95% CI, 0.97–2.25), The cohort found that the higher risk of twin birth for folate use (OR, 1.59; 95%: 1.41–1.78) was attenuated once potential misclassification was accounted for (OR, 1.02, 95% CI, 0.85–1.24)	Consistent Imprecise	Undetected	Fair	Low event rate, wide confidence intervals	Moderate for no effect	Generally applicable to primary care
	Childhood asthma, wheezing, allergy (2 SRs, 7 observational studies)	No effect for a large majority of comparisons and outcomes	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 RCT)	Increased risk for weight gain, diarrhea, constipation; reduced risk for irregular defecation; no difference for increased appetite, lack of appetite, exanthema, heartburn, and vertigo	Consistency unknown, single study, imprecise	Undetected		Low event rate, wide confidence intervals	Low for no effect	Generally applicable to primary care

Table 15. Summary of evidence for folic acid supplementation (continued)

Key Question	Number of Studies (Study Designs)	Summary of Findings	Consistency/ Precision	Reporting Bias	Overall Quality	Body of Evidence Limitations	EPC Assessment of Strength of Evidence for Key Question	Applicability
KQ 2 b: Differences in harms associated with folic acid supplementation by dosage, timing, and duration	Dosage: 1 SR, 1 observational study Duration: 0 Timing of asthma, wheezing, allergy (1 SRs, 3 observational studies)	Dosage: no consistent increase in the risk of childhood asthma, wheeze, or allergies by dosage Duration: none Timing: no consistent increase in the risk of childhood asthma, wheeze, or allergies by timing	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

CI = confidence interval; EPC = Evidence-based Practice Center; KQ = Key Question; NTD = neural tube defect; OR = odds ratio; RCT = randomized controlled trial; SR = Systematic Review.

Table 16. Estimates of folate sufficiency

Data Source	Population	What was Measured	Measure	Results
NHANES 2003-2006[42]	Nonpregnant women ages 15-44	• Two 24-hours dietary recalls; accounts for within individual variation • FA values assigned to foods using USDA National Nutrient Database for Standard Reference • Dietary supplement use in past 30 days, no. of days taken; recorded info on dosage from bottles; calculated average daily intake	Recommended daily allowance (≥400µg/day)	23.8% consuming recommended amount (≥400µg/day) (76.2% of women not consuming recommended amount)
NHANES 1999-2000[110]	Women ages 15-44	• Food and supplements • One 24 hour dietary recall • Included only subjects who had complete data for food folate and supplemental FA • Adjusted for measurement error using a subsample of NHANES III subjects who had provided 2 separate 24 hours recalls • Supplement intake over 1 month	% women ages 15-44 years consuming > 400 µg/day	Non-Hispanic White: 39% Non-Hispanic Black: 26% Mexican American: 28% (61-74% not consuming recommended amount)
NHANES 2007-2012[39]	Nonpregnant women ages 15-44	• Two 24-hour dietary recalls • RBC folate concentrations from analysis of blood samples using microbiologic assay method from 2007-2012 • Optimal RBC folate concentrations established by WHO to be >906 nmol/L (400 ng/L). For purposes of this analysis considered an optimal RBD folate concentration to be 748 nmol/L NHANES assay, the concentrations associated with an NTD risk of <9 NTDS per 10,000 live births based on the Daly et al.[47a] and Crider et al.[37b] studies	Percentage of women with RBC folate concentration associated with an NTD prevalence of ≥9 per 10,000 live births	22.8% of women of have suboptimal RBC folate concentrations for NTD prevention

RBC = red blod cells; FA = folic acid; NHANES = National Health and Nutrition Examination Survey; ng/L = nanograms/liter nmol/L = nanomole/liter; NTD = neural tube defect; USDA = United States Department of Agriculture; WHO = World Health Organization; µg = microgram

[a] Daly et al. 1995 reported that with RBC folate >906 nmol/L, the risk of NTD was 0.8 (95% CI: 0.43 to 1.5 with RBC folate between -0-339 nmol/L, the risk was over 8 times higher at 6.6. (95% CI: 3.3 to 11.7).[47]

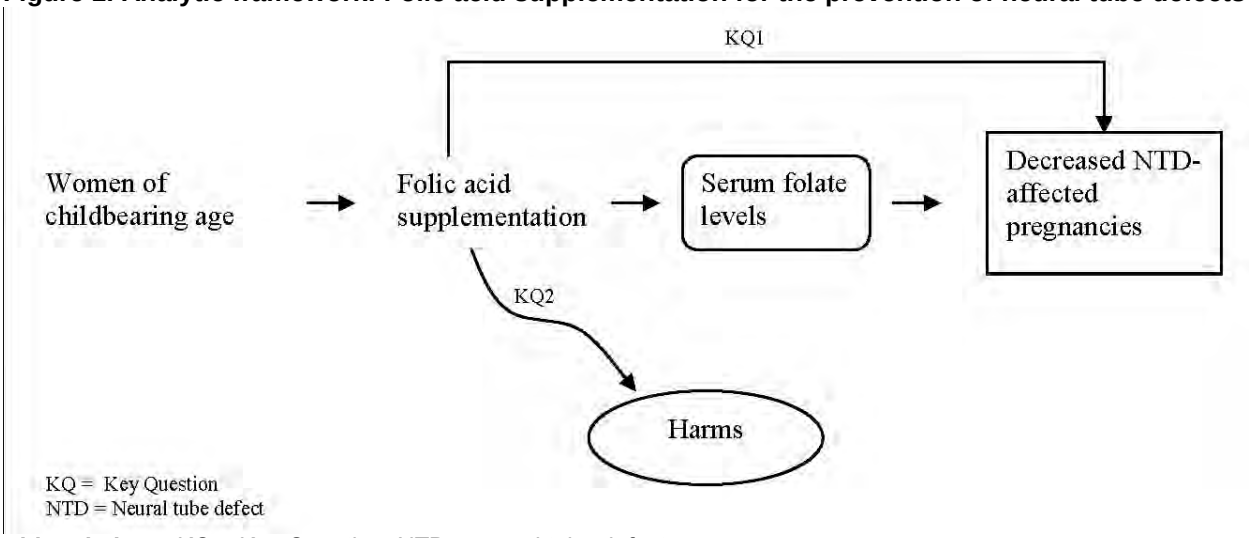
[b] Crider et al. 2014 estimated a risk of NTD at the lowest estimated RBC folate concertation of 500 nmol/L at 25.4 NTDs per 10,000 births and 6 NTDs per 10,000 births at 1180 nmol/L, which they note likely corresponds to the lowest feasible prevalence of NTDs that can be obtained with folic acid based interventions.[37]

Table 16. Estimates of folate sufficiency (continued)

Data Source	Population	What was Measured	Measure	Results
NHANES 2003-2006[135]	Women ages 14+ (pregnant and lactating women excluded)	• Dietary folate (measured by 2 24-hours recalls) and supplements (collected with 30-day frequency questionnaire) • Bias-corrected best power method to adjust for within-person variability • Dietary and total nutrient intakes estimated in 2 ways: (1) dietary and total folate in DFA and (2) dietary and total folic acid in micrograms, because the Dietary Reference Intakes are constructed in this manner. The estimated average requirement (EAR) is for folate DFE. • EAR for individuals age 14-18 years is 330 dietary folate equivalents (DFE) and for individuals ≥19 is 320 DEF	% of women below the EAR	Ages 14-18 – 19% 19-30 – 16.9% 31-50 – 14.6%
NHANES 2007-2010	Women ages 14-50	• Total usual intake from food, beverages, and dietary supplements • 1 day dietary recall and 30 day supplement questionnaire • Folate measured in dietary folate equivalents (DFE)	% of women below EAR: 3	Ages[136] 14-18 – 19% 19-30 – 11% 31-50 – 13%

NHANES = National Health and Nutrition Examination Survey

Figure 1. Analytic framework: Folic acid supplementation for the prevention of neural tube defects



Abbreviations: KQ = Key Question; NTD = neural tube defect.

Figure 2. Preferred reporting of systematic review and meta-analysis (PRISMA) tree

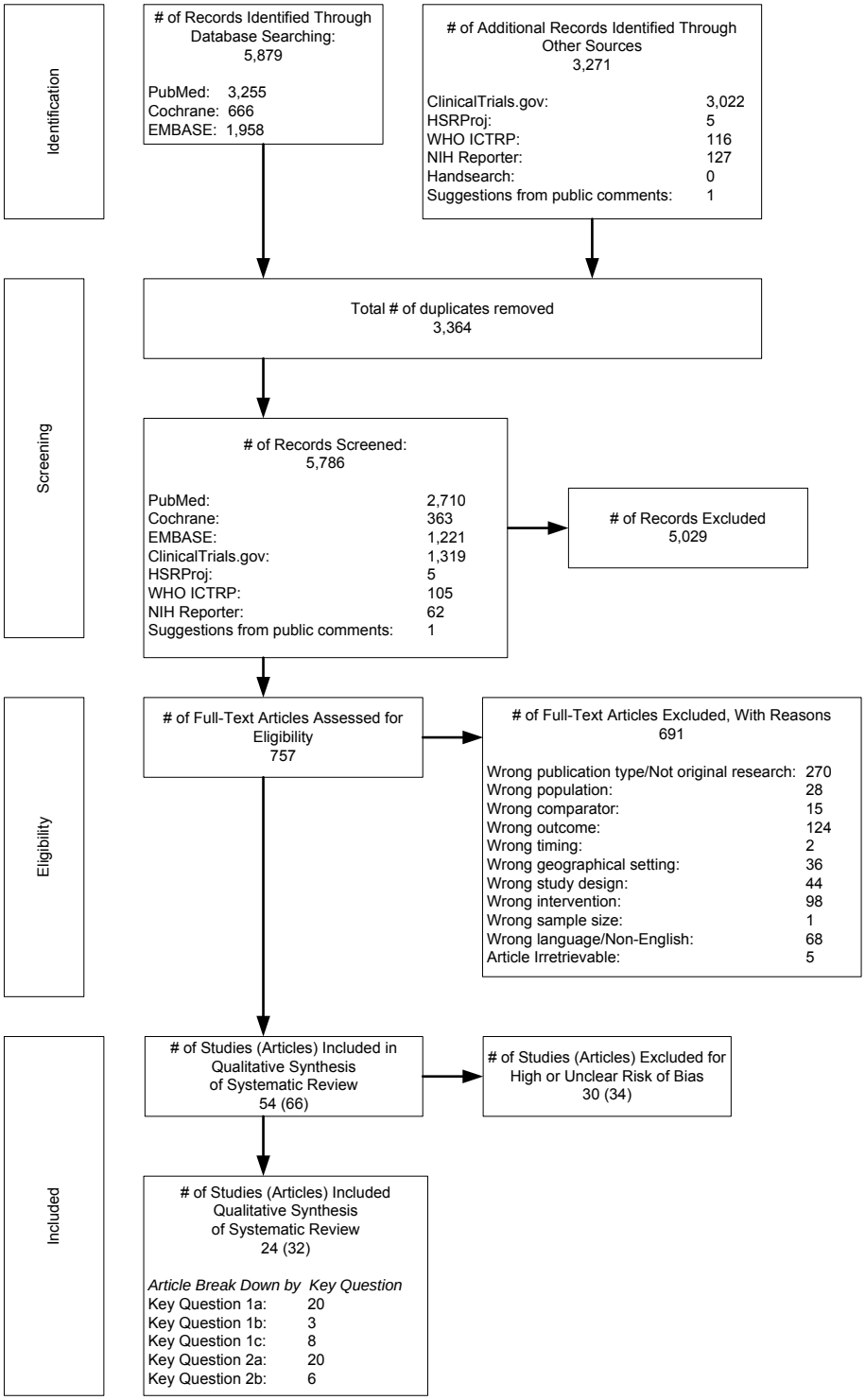
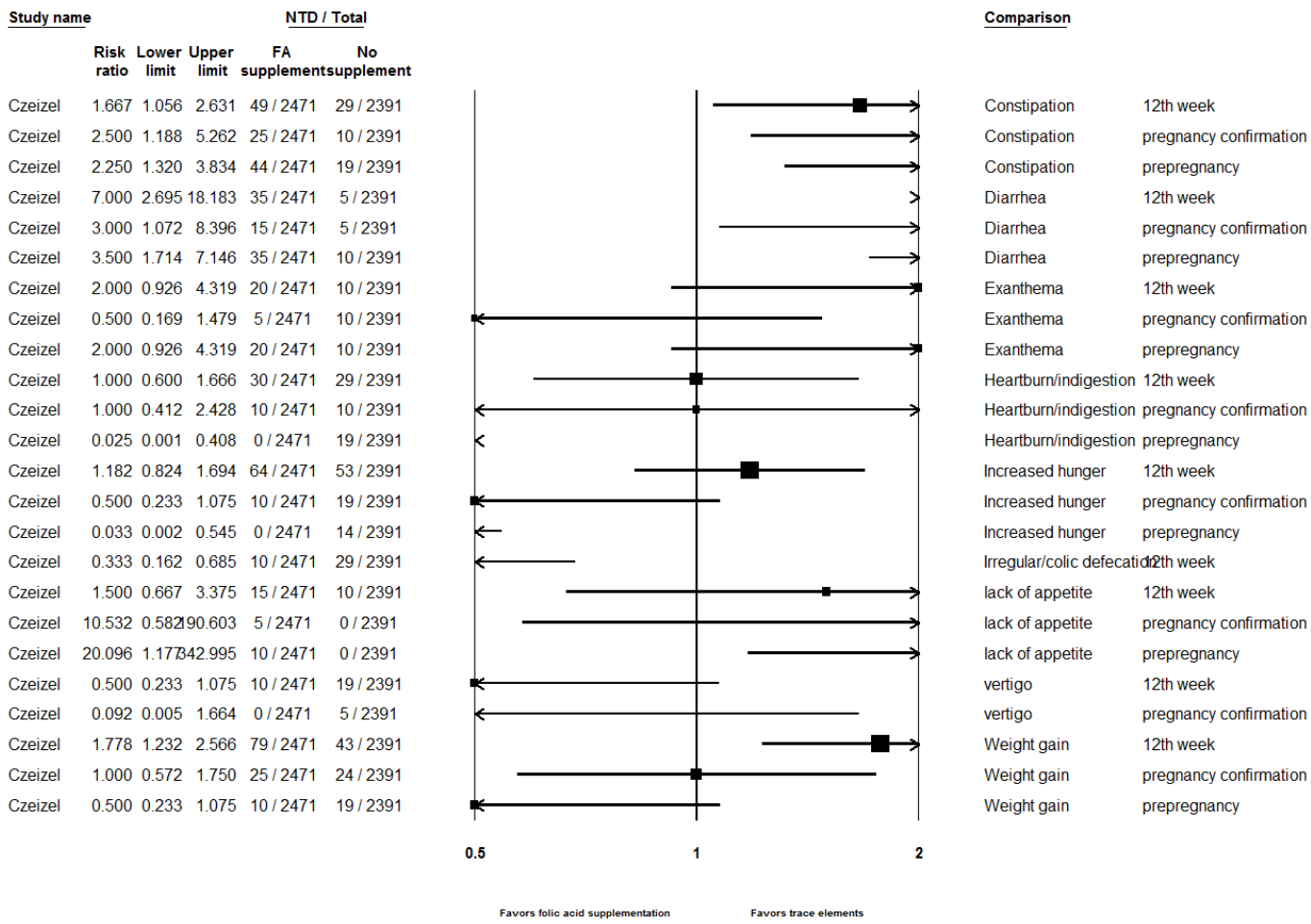
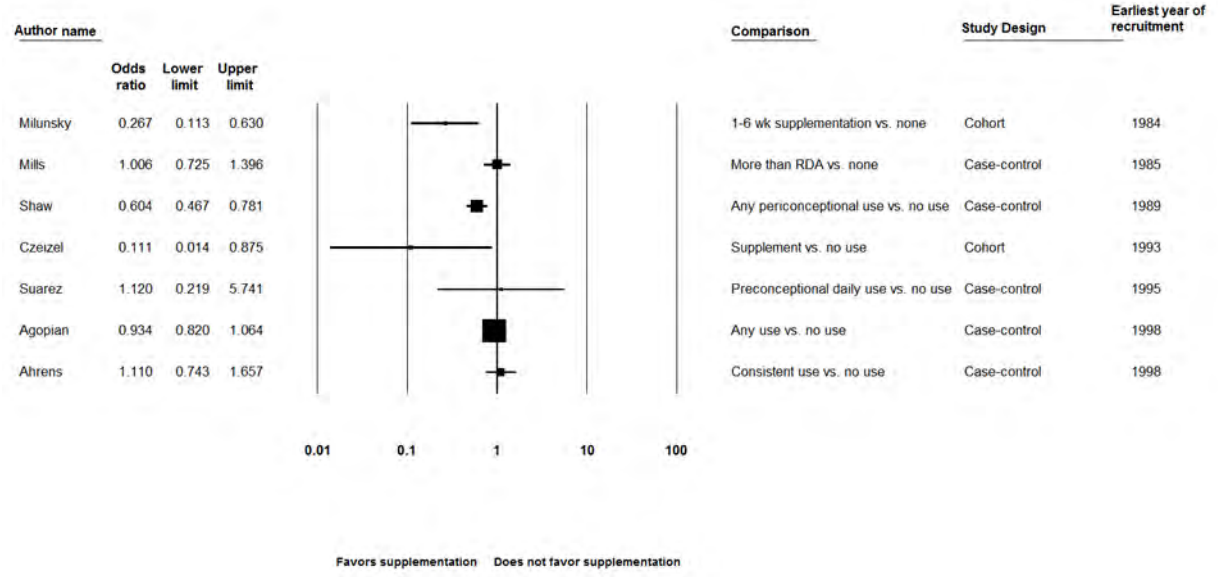


Figure 3. Folic acid supplementation and adverse events: Forest plot



Czeizel AE. Periconceptional folic acid containing multivitamin supplementation. Eur J Obstet Gynecol Reprod Biol. 1998 Jun;78(2):151-61. Epub: 1998/06/11. PMID: 9622312.

Figure 4. Folic acid supplementation and neural tube defects by earliest year of recruitment: Forest plot



Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA. 1989 Nov 24;262(20):2847-52. Epub: 1989/11/24. PMID: 2478730.

Mills JL, Rhoads GG, Simpson JL, et al. The absence of a relation between the periconceptional use of vitamins and neural-tube defects. National Institute of Child Health and Human Development Neural Tube Defects Study Group. N Engl J Med. 1989 Aug 17;321(7):430-5. Epub: 1989/08/17. PMID: 2761577.

Shaw GM, Schaffer D, Velie EM, et al. Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. Epidemiology. 1995 May;6(3):219-26. Epub: 1995/05/01. PMID: 7619926.

Czeizel AE, Dobo M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. Birth Defects Res A Clin Mol Teratol. 2004 Nov;70(11):853-61. Epub: 2004/11/04. PMID: 15523663.

Suarez L, Hendricks KA, Cooper SP, et al. Neural tube defects among Mexican Americans living on the US-Mexico border: effects of folic acid and dietary folate. Am J Epidemiol. 2000 Dec 1;152(11):1017-23. Epub: 2000/12/16. PMID: 11117610.

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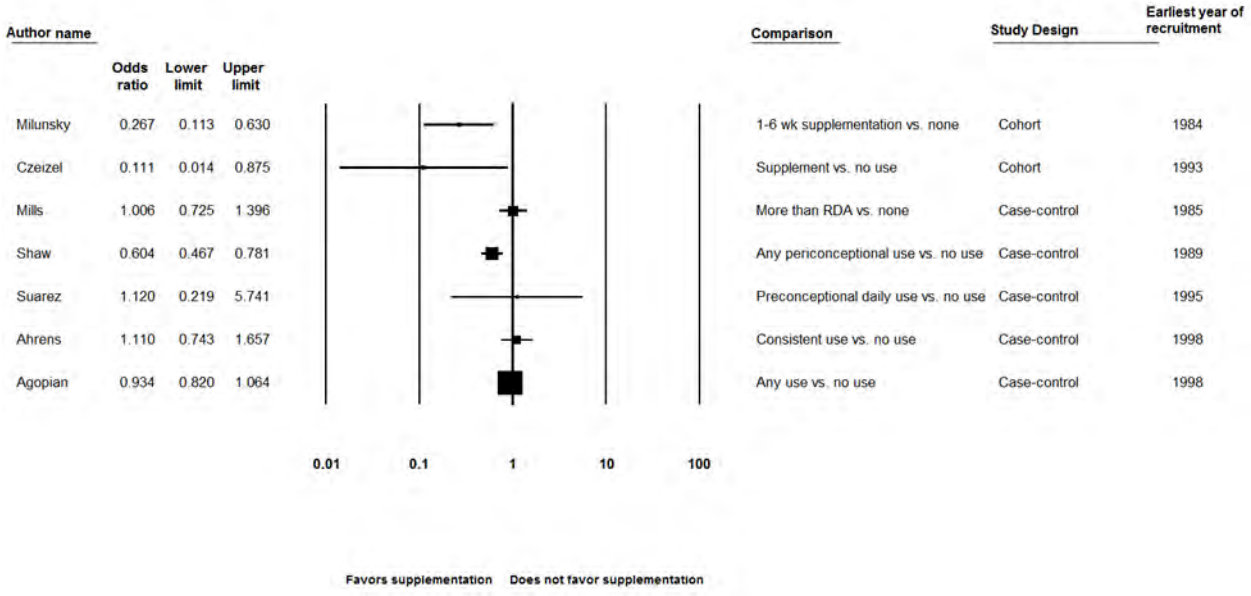
Figure 5. Folic acid supplementation and neural tube defects by study design: Forest plot



Milunsky A, Jick H, Jick SS, et al. Multivitamin/folic acid supplementation in early pregnancy reduces the prevalence of neural tube defects. JAMA. 1989 Nov 24;262(20):2847-52. Epub: 1989/11/24. PMID: 2478730.

Czeizel AE, Dobo M, Vargha P. Hungarian cohort-controlled trial of periconceptional multivitamin supplementation shows a reduction in certain congenital abnormalities. Birth Defects Res A Clin Mol Teratol. 2004 Nov;70(11):853-61. Epub: 2004/11/04. PMID: 15523663.

Mills JL, Rhoads GG, Simpson JL, et al. The absence of a relation between the periconceptional use of vitamins and neural-tube defects. National Institute of Child Health and Human Development Neural Tube Defects Study Group. N Engl J Med. 1989 Aug 17;321(7):430-5. Epub: 1989/08/17. PMID: 2761577.

Shaw GM, Schaffer D, Velie EM, et al. Periconceptional vitamin use, dietary folate, and the occurrence of neural tube defects. Epidemiology. 1995 May;6(3):219-26. Epub: 1995/05/01. PMID: 7619926.

Suarez L, Hendricks KA, Cooper SP, et al. Neural tube defects among Mexican Americans living on the US-Mexico border: effects of folic acid and dietary folate. Am J Epidemiol. 2000 Dec 1;152(11):1017-23. Epub: 2000/12/16. PMID: 11117610.

Ahrens K, Yazdy MM, Mitchell AA, et al. Folic acid intake and spina bifida in the era of dietary folic acid fortification. Epidemiology. 2011 Sep;22(5):731-7. Epub: 2011/06/11. PMID: 21659881.

Agopian AJ, Tinker SC, Lupo PJ, et al. Proportion of neural tube defects attributable to known risk factors. Birth Defects Res A Clin Mol Teratol. 2013 Jan;97(1):42-6. Epub: 2013/02/22. PMID: 23427344.

Appendix A. Search Strategy and Detailed Methods

6/23/14 PubMed Benefits Search

Search	Query	Items found
#1	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	786032
#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw])	46413
#3	Search (multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields])	4154
#4	Search ("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw])	27529
#5	Search (#1 AND (#2 OR #3) AND #4)	1794
#6	Search (#1 AND (#2 OR #3) AND #4) Filters: Humans	1623
#7	Search (#1 AND (#2 OR #3) AND #4) Filters: Other Animals	201
#8	Search (#7 NOT #6)	96
#9	Search (#5 NOT #8)	1698

9/4/14 PubMed Benefits Addendum Search
Added: "5-methyltetrahydropteroylpentaglutamate" [Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"

Search	Query	Items found
#1	Search (5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR 5-methyltetrahydropteroylpentaglutamate" [Supplementary Concept] OR 5-methyltetrahydrofolate triglutamate" [Supplementary Concept])	2015
#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields])	50052
#3	Search (#1 NOT #2)	534
#4	Search ("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw])	27715
#5	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	792595
#6	Search (#3 and #4 and #5)	5
#7	Search (#3 and #4 and #5) Filters: Humans	4
#8	Search (#3 and #4 and #5) Filters: Other Animals	3
#9	Search (#8 NOT #7)	1
#10	Search (#6 NOT #9)	4

11/10/14 PubMed Benefits Search

Search	Query	Items found
#1	Search ((Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH]))	797377
#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR "5-Me-THF" OR "5-Me-H4F" OR "5-methyltetrahydrofolate" OR "5-methyltetrahydropteroylpentaglutamate"[Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"[Supplementary Concept])	47728
#3	Search ((multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields]))	4245
#4	Search (("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw]))	27869
#5	Search ((#1 AND (#2 OR #3) AND #4))	1821
#6	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Humans	1647
#7	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Other Animals	207
#8	Search ((#7 NOT #6))	97
#9	Search (#5 NOT #8)	1724
#10	Search ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	28946
#11	Search (#9 and #10)	1
#13	Search (#5 NOT #8) Filters: Publication date from 2013/06/23	88

3/24/15 PubMed Benefits Search

Search	Query	Items found
#1	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	807095
#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR "5-Me-THF" OR "5-Me-H4F" OR "5-methyltetrahydrofolate" OR "5-methyltetrahydropteroylpentaglutamate"[Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"[Supplementary Concept])	48429
#3	Search (multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields])	4335
#4	Search ("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw])	28158
#5	Search ((#1 AND (#2 OR #3) AND #4))	1855
#6	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Humans	1669
#7	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Other Animals	211
#8	Search (#7 not #6)	99
#9	Search (#5 not #8)	1756
#10	Search ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	30021
#11	Search (#9 and #10)	1
#12	Search (#5 not #8) Filters: Publication date from 2014/05/10	55

7/27/15 PubMed Benefits Search

Search	Query	Items found
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#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR "5-Me-THF" OR "5-Me-H4F" OR "5-methyltetrahydrofolate" OR "5-methyltetrahydropteroylpentaglutamate"[Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"[Supplementary Concept])	49245
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#7	Search (#1 AND (#2 OR #3) AND #4) Filters: Other Animals	213
#8	Search (#7 NOT #6)	100
#9	Search (#5 NOT #8)	1780
#10	Search ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	34641
#11	Search (#9 and #10) Retraction Search	**1**
#12	Search (#5 NOT #8) Filters: Publication date from 2014/10/24	**49**

11/18/15 PubMed Benefits Search

Search	Query	Items found
#1	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	826665
#2	Search ("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR "5-Me-THF" OR "5-Me-H4F" OR "5-methyltetrahydrofolate" OR "5-methyltetrahydropteroylpentaglutamate"[Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"[Supplementary Concept]))	49896
#3	Search (multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields])	4490
#4	Search ("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw])	28752
#5	Search (#1 AND (#2 OR #3) AND #4)	1906
#6	Search (#1 AND (#2 OR #3) AND #4) Filters: Humans	1707
#7	Search (#1 AND (#2 OR #3) AND #4) Filters: Other Animals	213
#8	Search (#7 NOT #6)	100
#9	Search (#5 NOT #8)	1806
#10	Search ("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	38379
#11	Search (#9 and #10) Retraction	**1**
#12	Search (#5 NOT #8) Filters: Publication date from 2015/02/27	**48**

1/28/16 PubMed Benefits Search

Search	Query	Items found
#1	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	854509
#2	Search (("folic acid"[MeSH] OR "vitamin b9"[tw] OR "vitamin m"[tw] or "Pteroylglutamic Acid"[tw] OR "folvite"[tw] OR "folacin"[tw] OR "folate"[tw] OR "folic acid"[tw] OR "5-Me-THF" OR "5-Me-H4F" OR "5-methyltetrahydrofolate" OR "5-methyltetrahydropteroylpentaglutamate"[Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate"[Supplementary Concept]))	51191
#3	Search ((multivitamin[all fields] OR "prenatal vitamin"[all fields] OR multivitamins[all fields] OR "prenatal vitamins"[all fields] OR "vitamin supplement"[all fields] OR "vitamin supplements"[all fields]))	4536
#4	Search (("neural tube defects"[MeSH Terms] OR "spina bifida"[All Fields] OR "neural tube damage"[All Fields] OR "neural tube defect"[All Fields] OR "neural tube defects"[All Fields] OR "neural tube disorders"[All Fields] OR "Neural tube defect, folate-sensitive"[Supplementary Concept] OR Craniorachischisis[tw] OR Craniorachischises[tw] OR Diastematomyelia[tw] OR Diastematomyelias[tw] OR "Tethered Cord Syndrome"[tw] OR "Tethered Cord Syndromes"[tw] OR "Occult Spinal Dysraphism Sequence"[tw] OR "Tethered Spinal Cord Syndrome"[tw] OR "Occult Spinal Dysraphism"[tw] OR "Occult Spinal Dysraphisms"[tw] OR Iniencephaly[tw] OR Iniencephalies[tw] OR "Neurenteric Cyst"[tw] OR "Neurenteric Cysts"[tw] OR "Neuroenteric Cyst"[tw] OR "Neuroenteric Cysts"[tw] OR "Spinal Cord Myelodysplasia"[tw] OR "Spinal Cord Myelodysplasias"[tw] OR Acrania[tw] OR Acranias[tw] OR Exencephaly[tw] OR Exencephalies[tw]))	29292
#5	Search ((#1 AND (#2 OR #3) AND #4))	1923
#6	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Humans	1715
#7	Search ((#1 AND (#2 OR #3) AND #4)) Filters: Other Animals	216
#8	Search ((#7 NOT #6))	103
#9	Search ((#5 NOT #8))	1820
#10	Search (("retraction"[All Fields] OR "Retracted Publication"[pt] OR Duplicate Publication [PT] OR Erratum[All Fields]))	40500
#11	Search ((#9 and #10))	1
#12	Search ((#5 NOT #8)) Filters: Publication date from 2015/10/18	22

9/9/14 PubMed Harms Search

Search	Query	Items found
#1	Search "folic acid"[mesh] OR "folic acid"[tiab] OR "folvite"[tiab] OR "folacin"[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR "5-methyltetrahydropteroylpentaglutamate" [Supplementary Concept] OR "5-methyltetrahydrofolate triglutamate" [Supplementary Concept]	35919
#2	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR "pregnant women"[MeSH])	792843
#3	Search (#1 and #2)	5060
#4	Search ("Colorectal Neoplasms"[Mesh] OR ("Vitamin B 12 Deficiency"[Mesh] OR ("vitamin b 12"[MeSH Terms] AND deficien*[Text Word])) OR ("Vitamin B 6 Deficiency"[Mesh] OR ("vitamin b 6"[MeSH Terms] AND deficien*[Text Word])) OR ("Drug-Related Side Effects and Adverse Reactions"[Majr] OR "Patient Harm"[Majr] harm[tiab] OR harms[tiab] OR "adverse effect"[tiab] OR "adverse effects"[tiab] OR "adverse event"[tiab] OR "adverse events"[tiab] OR complication[tiab] OR complications[tiab]))	941528
#5	Search (#3 and #4)	681
#6	Search (#3 and #4) Filters: Humans	586
#7	Search (#3 and #4) Filters: Other Animals	90
#8	Search (#7 not #6)	47
#9	Search (#5 not #8)	**634**

11/11/14 PubMed Harms Search

Search	Query	Items found
#1	Search (“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept])	36189
#2	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH])	797435
#3	Search (#1 and #2)	5102
#4	Search “Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR “Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word]) OR “Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] harm[tiab] OR harms[tiab] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab]	952237
#5	Search ((#3 and #4))	689
#6	Search #5 Filters: Humans	592
#7	Search #5	689
#8	Search #5 Filters: Other Animals	93
#9	Search (#8 NOT #6)	49
#10	Search (#5 NOT #9)	640
#11	Search (#5 NOT #9) Filters: Publication date from 2013/09/09	30
#12	Search (“retraction”[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	28984
#13	Search (#5 and #12)	2

1/6/15 PubMed Harms Addendum Search

Search	Query	Items found
#4	Search “folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept]	36405
#5	Search ((Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH]))	801618
#6	Search (#4 and #5)	5145
#7	Search (“Twins”[mesh] OR “Pregnancy, Twin”[mesh] OR twinning OR twins)	39869
#8	Search (#6 and #7)	57
#9	Search ((“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR (“Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word])) OR (“Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] harm[tiab] OR harms[tiab] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab])))	962466
#10	Search (#8 NOT #9)	47
#11	Search (#8 NOT #9) Filters: Humans	46
#12	Search (#8 NOT #9) Filters: Other Animals	4
#13	Search (#12 NOT #11)	0
#14	Search (#10 NOT #13)	**47**

3/24/15 and 3/27/15 PubMed Harms Search

Search	Query	Items found
#23	Search (“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept])	36728
#24	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH])	807095
#25	Search (#23 and #24)	5210
#26	Search (“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR “Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word]) OR “Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] harm[tiab] OR harms[tiab] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab])	821329
#27	Search (#25 and #26)	332
#28	Search (#25 and #26) Filters: Humans	284
#29	Search (#25 and #26) Filters: Other Animals	42
#30	Search (#29 not #28)	21
#31	Search (#27 not #30)	311
#32	Search (#27 not #30) Filters: Publication date from 2014/05/10	11
#33	Search (“retraction”[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	30021
#34	Search (#27 and #33)	0

6/10/15 PubMed Harms Addendum Search

Search	Query	Items found
#1	Search ((Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH]))	813856
#2	Search ((“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept]))	37102
#3	Search (#1 and #2)	5261
#4	Search “Asthma”[Mesh]	107710
#5	Search asthma	150552
#6	Search (#4 or #5)	150552
#7	Search “adverse effects” [Subheading]	1765128
#8	Search (#3 and #6)	22
#9	Search (#3 and #7)	779
#10	Search (#8 or #9)	788
#11	Search (#8 or #9) Filters: Humans	671
#12	Search (#8 or #9) Filters: Other Animals	195
#13	Search (#12 not #11)	114
#14	Search (#10 not #13)	674
#15	Search ((“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR (“Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word])) OR (“Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] harm[tiab] OR harms[tiab] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab])	992424
#16	Search (#14 NOT #15)	**562**

7/27/15 PubMed Harms Search

Search	Query	Items found
#1	Search (“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept])	37694
#2	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH])	817957
#3	Search (#1 and #2)	5319
#4	Search ((“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR (“Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word])) OR (“Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] OR harm[tiab] OR harms[tiab] OR “adverse effects” [Subheading] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab]) OR “Twins”[mesh] OR “Pregnancy, Twin”[mesh] OR twinning OR twins OR asthma[Mesh] OR asthma))	2779068
#5	Search (#3 and #4)	1499
#6	Search (#3 and #4) Filters: Humans	1228
#7	Search (#3 and #4) Filters: Other Animals	271
#8	Search (#7 NOT #6)	158
#9	Search (#5 NOT #8)	1341
#10	Search (#5 NOT #8) Filters: Publication date from 2014/07/06	**40**
#11	Search (“retraction”[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	34641
#12	Search (#5 and #11) Retractions	**2**

11/18/15 PubMed Harms Search

Search	Query	Items found
#1	Search (“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept])	38183
#2	Search (Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH])	826665
#3	Search (#1 and #2)	5404
#4	Search ((“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR (“Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word])) OR (“Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] OR harm[tiab] OR harms[tiab] OR “adverse effects” [Subheading] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab]) OR “Twins”[mesh] OR “Pregnancy, Twin”[mesh] OR twinning OR twins OR asthma[Mesh] OR asthma))	2822126
#5	Search (#3 and #4)	1522
#6	Search (#3 and #4) Filters: Humans	1243
#7	Search (#3 and #4) Filters: Other Animals	275
#8	Search (#7 NOT #6)	161
#9	Search (#5 not #8)	1361
#10	Search (#5 not #8) Filters: Publication date from 2015/02/27	23
#11	Search (“retraction”[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [PT] OR Erratum[All Fields])	38379
#12	Search (#5 and #11)	2

1/28/16 PubMed Harms Search

Search	Query	Items found
#1	Search ((“folic acid”[mesh] OR “folic acid”[tiab] OR “folvite”[tiab] OR “folacin”[tiab] OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate OR “5-methyltetrahydropteroylpentaglutamate” [Supplementary Concept] OR “5-methyltetrahydrofolate triglutamate” [Supplementary Concept]))	39456
#2	Search ((Pregnancy[MeSH] OR pregnancy[tw] OR pregnant[tw] OR “pregnant women”[MeSH]))	854509
#3	Search ((#1 and #2))	5507
#4	Search (((“Colorectal Neoplasms”[Mesh] OR (“Vitamin B 12 Deficiency”[Mesh] OR (“vitamin b 12”[MeSH Terms] AND deficien*[Text Word])) OR (“Vitamin B 6 Deficiency”[Mesh] OR (“vitamin b 6”[MeSH Terms] AND deficien*[Text Word])) OR (“Drug-Related Side Effects and Adverse Reactions”[Majr] OR “Patient Harm”[Majr] OR harm[tiab] OR harms[tiab] OR “adverse effects” [Subheading] OR “adverse effect”[tiab] OR “adverse effects”[tiab] OR “adverse event”[tiab] OR “adverse events”[tiab] OR complication[tiab] OR complications[tiab]) OR “Twins”[mesh] OR “Pregnancy, Twin”[mesh] OR twinning OR twins OR asthma[Mesh] OR asthma)))	2852040
#5	Search ((#3 and #4))	1545
#6	Search ((#3 and #4)) Filters: Humans	1324
#7	Search ((#3 and #4)) Filters: Other Animals	279
#8	Search ((#7 NOT #6))	164
#9	Search ((#5 not #8))	1381
#10	Search ((#5 not #8)) Filters: Publication date from 2015/10/18	10
#11	Search ((“retraction”[All Fields] OR “Retracted Publication”[pt] OR Duplicate Publication [PT] OR Erratum[All Fields]))	40500
#12	Search ((#5 and #11))	2

6/23/14 Cochrane Benefits Search

Search	Query	Items found
#1	[mh Pregnancy] OR pregnancy OR pregnant OR [mh “pregnant women”]	27927
#2	[mh “folic acid”] OR “vitamin b9” OR “vitamin m” or “Pteroylglutamic Acid” OR “folvite” OR “folacin” OR “folate” OR “folic acid”	3775
#3	Multivitamin OR “prenatal vitamin” OR multivitamins OR “prenatal vitamins” OR “vitamin supplement” OR “vitamin supplements”	915
#4	[mh “neural tube defects”] OR “spina bifida” OR “neural tube damage” OR “neural tube defect” OR “neural tube defects” OR “neural tube disorders” OR “Neural tube defect, folate-sensitive” OR Craniorachischisis OR Craniorachischises OR Diastematomyelia OR Diastematomyelias OR “Tethered Cord Syndrome” OR “Tethered Cord Syndromes” OR “Occult Spinal Dysraphism Sequence” OR “Tethered Spinal Cord Syndrome” OR “Occult Spinal Dysraphism” OR “Occult Spinal Dysraphisms” OR Iniencephaly OR Iniencephalies OR “Neurenteric Cyst” OR “Neurenteric Cysts” OR “Neuroenteric Cyst” OR “Neuroenteric Cysts” OR “Spinal Cord Myelodysplasia” OR “Spinal Cord Myelodysplasias” OR Acrania OR Acranias OR Exencephaly OR Exencephalies	374
#5	Search (#1 AND (#2 OR #3) AND #4)	**105**

9/4/14 Cochrane Benefits Addendum Search

ID	Search	Hits
#1	5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or 5-methyltetrahydropteroylpentaglutamate or “5-methyltetrahydrofolate triglutamate”	96
#2	[mh “folic acid”] or “vitamin b9” or “vitamin m” or “Pteroylglutamic Acid” or “folvite” or “folacin” or “folate” or “folic acid” or Multivitamin or “prenatal vitamin” or multivitamins or “prenatal vitamins” or “vitamin supplement” or “vitamin supplements”	4467
#3	#1 not #2	16
#4	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	28255
#5	#3 and #4	2
#6	[mh “neural tube defects”] or “spina bifida” or “neural tube damage” or “neural tube defect” or “neural tube defects” or “neural tube disorders” or “Neural tube defect, folate-sensitive” or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or “Tethered Cord Syndrome” or “Tethered Cord Syndromes” or “Occult Spinal Dysraphism Sequence” or “Tethered Spinal Cord Syndrome” or “Occult Spinal Dysraphism” or “Occult Spinal Dysraphisms” or Iniencephaly or Iniencephalies or “Neurenteric Cyst” or “Neurenteric Cysts” or “Neuroenteric Cyst” or “Neuroenteric Cysts” or “Spinal Cord Myelodysplasia” or “Spinal Cord Myelodysplasias” or Acrania or Acranias or Exencephaly or Exencephalies	376
#7	#5 and #6	0

11/11/14 Cochrane Benefits Search

ID	Search	
#1	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	29122
#2	[mh “folic acid”] or “vitamin b9” or “vitamin m” or “Pteroylglutamic Acid” or “folvite” or “folacin” or “folate” or “folic acid” or 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate	3909
#3	Multivitamin or “prenatal vitamin” or multivitamins or “prenatal vitamins” or “vitamin supplement” or “vitamin supplements”	944
#4	[mh “neural tube defects”] or “spina bifida” or “neural tube damage” or “neural tube defect” or “neural tube defects” or “neural tube disorders” or “Neural tube defect, folate-sensitive” or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or “Tethered Cord Syndrome” or “Tethered Cord Syndromes” or “Occult Spinal Dysraphism Sequence” or “Tethered Spinal Cord Syndrome” or “Occult Spinal Dysraphism” or “Occult Spinal Dysraphisms” or Iniencephaly or Iniencephalies or “Neurenteric Cyst” or “Neurenteric Cysts” or “Neuroenteric Cyst” or “Neuroenteric Cysts” or “Spinal Cord Myelodysplasia” or “Spinal Cord Myelodysplasias” or Acrania or Acranias or Exencephaly or Exencephalies	383
#5	(#1 and (#2 or #3) and #4)	108
# 6	(#1 and (#2 or #3) and #4) Publication Year from 2013 to 2014	16

3/24/15 Cochrane Benefits Search

ID	Search	Hits
#1	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	29687
#2	[mh "folic acid"] or "vitamin b9" or "vitamin m" or "Pteroylglutamic Acid" or "folvite" or "folacin" or "folate" or "folic acid" or 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate	4051
#3	Multivitamin or "prenatal vitamin" or multivitamins or "prenatal vitamins" or "vitamin supplement" or "vitamin supplements"	988
#4	[mh "neural tube defects"] or "spina bifida" or "neural tube damage" or "neural tube defect" or "neural tube defects" or "neural tube disorders" or "Neural tube defect, folate-sensitive" or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or "Tethered Cord Syndrome" or "Tethered Cord Syndromes" or "Occult Spinal Dysraphism Sequence" or "Tethered Spinal Cord Syndrome" or "Occult Spinal Dysraphism" or "Occult Spinal Dysraphisms" or Iniencephaly or Iniencephalies or "Neurenteric Cyst" or "Neurenteric Cysts" or "Neuroenteric Cyst" or "Neuroenteric Cysts" or "Spinal Cord Myelodysplasia" or "Spinal Cord Myelodysplasias" or Acrania or Acranias or Exencephaly or Exencephalies	392
#5	(#1 and (#2 or #3) and #4)	108
#6	(#1 and (#2 or #3) and #4) Publication Year from 2014 to 2015	8

7/27/15 Cochrane Benefits Search

ID	Search	Hits
#1	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	30805
#2	[mh "folic acid"] or "vitamin b9" or "vitamin m" or "Pteroylglutamic Acid" or "folvite" or "folacin" or "folate" or "folic acid" or 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate 4051	4253
#3	Multivitamin or "prenatal vitamin" or multivitamins or "prenatal vitamins" or "vitamin supplement" or "vitamin supplements"	1065
#4	[mh "neural tube defects"] or "spina bifida" or "neural tube damage" or "neural tube defect" or "neural tube defects" or "neural tube disorders" or "Neural tube defect, folate-sensitive" or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or "Tethered Cord Syndrome" or "Tethered Cord Syndromes" or "Occult Spinal Dysraphism Sequence" or "Tethered Spinal Cord Syndrome" or "Occult Spinal Dysraphism" or "Occult Spinal Dysraphisms" or Iniencephaly or Iniencephalies or "Neurenteric Cyst" or "Neurenteric Cysts" or "Neuroenteric Cyst" or "Neuroenteric Cysts" or "Spinal Cord Myelodysplasia" or "Spinal Cord Myelodysplasias" or Acrania or Acranias or Exencephaly or Exencephalies	408
#5	(#1 and (#2 or #3) and #4)	115
#6	(#1 and (#2 or #3) and #4) Publication Year from 2014 to 2015	**13**

11/18/15 Cochrane Benefits Search

ID	Search	Hits
#1	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	31487
#2	[mh "folic acid"] or "vitamin b9" or "vitamin m" or "Pteroylglutamic Acid" or "folvite" or "folacin" or "folate" or "folic acid" or 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate 4051	4353
#3	Multivitamin or "prenatal vitamin" or multivitamins or "prenatal vitamins" or "vitamin supplement" or "vitamin supplements"	1098
#4	[mh "neural tube defects"] or "spina bifida" or "neural tube damage" or "neural tube defect" or "neural tube defects" or "neural tube disorders" or "Neural tube defect, folate-sensitive" or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or "Tethered Cord Syndrome" or "Tethered Cord Syndromes" or "Occult Spinal Dysraphism Sequence" or "Tethered Spinal Cord Syndrome" or "Occult Spinal Dysraphism" or "Occult Spinal Dysraphisms" or Iniencephaly or Iniencephalies or "Neurenteric Cyst" or "Neurenteric Cysts" or "Neuroenteric Cyst" or "Neuroenteric Cysts" or "Spinal Cord Myelodysplasia" or "Spinal Cord Myelodysplasias" or Acrania or Acranias or Exencephaly or Exencephalies	411
#5	(#1 and (#2 or #3) and #4) Publication Year from 2014 to 2015	**16**

1/28/16 Cochrane Benefits Search

ID	Search	Hits
#1	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	32013
#2	[mh "folic acid"] or "vitamin b9" or "vitamin m" or "Pteroylglutamic Acid" or "folvite" or "folacin" or "folate" or "folic acid" or 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate 4051	4403
#3	Multivitamin or "prenatal vitamin" or multivitamins or "prenatal vitamins" or "vitamin supplement" or "vitamin supplements"	1115
#4	[mh "neural tube defects"] or "spina bifida" or "neural tube damage" or "neural tube defect" or "neural tube defects" or "neural tube disorders" or "Neural tube defect, folate-sensitive" or Craniorachischisis or Craniorachischises or Diastematomyelia or Diastematomyelias or "Tethered Cord Syndrome" or "Tethered Cord Syndromes" or "Occult Spinal Dysraphism Sequence" or "Tethered Spinal Cord Syndrome" or "Occult Spinal Dysraphism" or "Occult Spinal Dysraphisms" or Iniencephaly or Iniencephalies or "Neurenteric Cyst" or "Neurenteric Cysts" or "Neuroenteric Cyst" or "Neuroenteric Cysts" or "Spinal Cord Myelodysplasia" or "Spinal Cord Myelodysplasias" or Acrania or Acranias or Exencephaly or Exencephalies	414
#5	(#1 and (#2 or #3) and #4) Online Publication Date from Oct 2015	5

9/9/14 Cochrane Harms Search

ID	Search Terms	Hits
#1	[mh "folic acid"] or "folic acid" or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or "5-methyltetrahydropteroylpentaglutamate" or "5-methyltetrahydrofolate triglutamate"	3438
#2	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	28256
#3	#1 and #2	579
#4	[mh Twins] or [mh "Pregnancy, Twin"] or twinning or twins or [mh "Colorectal Neoplasms"] or ([mh "Vitamin B 12 Deficiency"] or ([mh "vitamin b 12"] and deficien*)) or ([mh "Vitamin B 6 Deficiency"] or ([mh "vitamin b 6"] and deficien*)) or ([mh "Drug-Related Side Effects and Adverse Reactions" [mj]] or [mh "Patient Harm" [mj]] or harm or harms or "adverse effect" or "adverse effects" or "adverse event" or "adverse events" or complication or complications)	217992
#5	#3 and #4	330

11/11/14 Cochrane Harms Search

ID	Search	Hits
#1	[mh "folic acid"] or "folic acid" or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or "5-methyltetrahydropteroylpentaglutamate" or "5-methyltetrahydrofolate triglutamate"	3511
#2	[mh Pregnancy] or pregnancy or pregnant or [mh "pregnant women"]	29122
#3	#1 and #2	598
#4	[mh Twins] or [mh "Pregnancy, Twin"] or twinning or twins or [mh "Colorectal Neoplasms"] or ([mh "Vitamin B 12 Deficiency"] or ([mh "vitamin b 12"] and deficien*)) or ([mh "Vitamin B 6 Deficiency"] or ([mh "vitamin b 6"] and deficien*)) or ([mh "Drug-Related Side Effects and Adverse Reactions" [mj]] or [mh "Patient Harm" [mj]] or harm or harms or "adverse effect" or "adverse effects" or "adverse event" or "adverse events" or complication or complications)	221497
#5	#3 and #4	338
#6	#3 and #4 Publication Year from 2013 to 2014	65

3/24/15 Cochrane Harms Search

ID	Search	Hits
#1	[mh “folic acid”] or “folic acid” or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or “5-methyltetrahydropteroylpentaglutamate” or “5-methyltetrahydrofolate triglutamate”	3650
#2	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	29687
#3	#1 and #2	627
#4	[mh Twins] or [mh “Pregnancy, Twin”] or twinning or twins or [mh “Colorectal Neoplasms”] or ([mh “Vitamin B 12 Deficiency”] or ([mh “vitamin b 12”] and deficien*)) or ([mh “Vitamin B 6 Deficiency”] or ([mh “vitamin b 6”] and deficien*)) or ([mh “Drug-Related Side Effects and Adverse Reactions” [mj]] or [mh “Patient Harm” [mj]] or harm or harms or “adverse effect” or “adverse effects” or “adverse event” or “adverse events” or complication or complications)	228315
#5	#3 and #4	338
#6	#3 and #4 Publication Year from 2014 to 2015	41

6/10/15 Cochrane Harms Addendum Search

ID	Search	Hits
#1	[mh “folic acid”] or “folic acid” or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or “5-methyltetrahydropteroylpentaglutamate” or “5-methyltetrahydrofolate triglutamate”	3752
#2	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	30578
#3	#1 and #2	649
#4	asthma	24345
#5	#3 and #4	22
#6	[mh /AE]	105460
#7	#3 and #6	73
#8	#5 or #7	84
#9	[mh Twins] or [mh “Pregnancy, Twin”] or twinning or twins or [mh “Colorectal Neoplasms”] or ([mh “Vitamin B 12 Deficiency”] or ([mh “vitamin b 12”] and deficien*)) or ([mh “Vitamin B 6 Deficiency”] or ([mh “vitamin b 6”] and deficien*)) or ([mh “Drug-Related Side Effects and Adverse Reactions” [mj]] or [mh “Patient Harm” [mj]] or harm or harms or “adverse effect” or “adverse effects” or “adverse event” or “adverse events” or complication or complications)	234745
#10	#8 not #9	0

7/27/15 Cochrane Harms Search

ID	Search	Hits
#1	[mh “folic acid”] or “folic acid” or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or “5-methyltetrahydropteroylpentaglutamate” or “5-methyltetrahydrofolate triglutamate”	3867
#2	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	30805
#3	#1 and #2	676
#4	[mh Twins] or [mh “Pregnancy, Twin”] or twinning or twins or [mh “Colorectal Neoplasms”] or ([mh “Vitamin B 12 Deficiency”] or ([mh “vitamin b 12”] and deficien*)) or ([mh “Vitamin B 6 Deficiency”] or ([mh “vitamin b 6”] and deficien*)) or ([mh “Drug-Related Side Effects and Adverse Reactions” [mj]] or [mh “Patient Harm” [mj]] or harm or harms or [mh /AE] or “adverse effect” or “adverse effects” or “adverse event” or “adverse events” or complication or complications or [mh Asthma] or asthma)	256428
#5	#3 and #4	366
#6	#3 and #4 Publication Year from 2014 to 2015	**56**

11/18/15 Cochrane Harms Search

ID	Search	Hits
#1	[mh “folic acid”] or “folic acid” or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or “5-methyltetrahydropteroylpentaglutamate” or “5-methyltetrahydrofolate triglutamate”	3962
#2	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	31487
#3	#1 and #2	710
#4	[mh Twins] or [mh “Pregnancy, Twin”] or twinning or twins or [mh “Colorectal Neoplasms”] or ([mh “Vitamin B 12 Deficiency”] or ([mh “vitamin b 12”] and deficien*)) or ([mh “Vitamin B 6 Deficiency”] or ([mh “vitamin b 6”] and deficien*)) or ([mh “Drug-Related Side Effects and Adverse Reactions” [mj]] or [mh “Patient Harm” [mj]] or harm or harms or [mh /AE] or “adverse effect” or “adverse effects” or “adverse event” or “adverse events” or complication or complications or [mh Asthma] or asthma)	261297
#5	#3 and #4 Publication Year from 2015 to 2015	44

1/28/16 Cochrane Harms Search

#1	**[mh “folic acid”] or “folic acid” or folvite or folacin 5-Me-THF or 5-Me-H4F or 5-methyltetrahydrofolate or “5-methyltetrahydropteroylpentaglutamate” or “5-methyltetrahydrofolate triglutamate”**	**4011**
#2	[mh Pregnancy] or pregnancy or pregnant or [mh “pregnant women”]	32013
#3	#1 and #2	722
#4	[mh Twins] or [mh “Pregnancy, Twin”] or twinning or twins or [mh “Colorectal Neoplasms”] or ([mh “Vitamin B 12 Deficiency”] or ([mh “vitamin b 12”] and deficien*)) or ([mh “Vitamin B 6 Deficiency”] or ([mh “vitamin b 6”] and deficien*)) or ([mh “Drug-Related Side Effects and Adverse Reactions” [mj]] or [mh “Patient Harm” [mj]] or harm or harms or [mh /AE] or “adverse effect” or “adverse effects” or “adverse event” or “adverse events” or complication or complications or [mh Asthma] or asthma)	263974
#5	#3 and #4 Online Publication Date from Oct 2015	16

6/23/14 EMBASE Benefits Search

No.	Query	Results
#11	#9 NOT #10	543
#10	#9 AND [medline]/lim	1,373
#9	#5 NOT #8	1,916
#8	#7 NOT #6 AND [animals]/lim	77
#7	#5 AND [animals]/lim	343
#6	#5 AND [humans]/lim	1,832
#5	#1 AND (#2 OR #3) AND #4	1,993
#4	‘spinal dysraphism’/exp OR ‘spinal dysraphism’ OR ‘neural tube damage’ OR ‘neural tube defect’/exp OR ‘neural tube defect’ OR ‘neural tube defects’/exp OR ‘neural tube defects’ OR ‘neural tube disorders’ OR ‘neural tube defect, folate-sensitive’ OR craniorachischisis OR craniorachischises OR ‘diastematomyelia’/exp OR diastematomyelia OR diastematomyelias OR ‘tethered cord syndrome’/exp OR ‘tethered cord syndrome’ OR ‘tethered cord syndromes’ OR ‘occult spinal dysraphism sequence’ OR ‘tethered spinal cord syndrome’ OR ‘occult spinal dysraphism’/exp OR ‘occult spinal dysraphism’ OR ‘occult spinal dysraphisms’ OR ‘iniencephaly’/exp OR iniencephaly OR iniencephalies OR ‘neurenteric cyst’ OR ‘neurenteric cysts’ OR ‘neuroenteric cyst’ OR ‘neuroenteric cysts’ OR ‘spinal cord myelodysplasia’ OR ‘spinal cord myelodysplasias’ OR acrania OR acranias OR ‘exencephaly’/exp OR exencephaly OR exencephalies	30,718
#3	‘multivitamin’/exp OR multivitamin OR ‘prenatal vitamin’ OR ‘multivitamins’/exp OR multivitamins OR ‘prenatal vitamins’ OR ‘vitamin supplement’ OR ‘vitamin supplements’	8,726
#2	‘vitamin b9’ OR ‘vitamin m’/exp OR ‘vitamin m’ OR ‘pteroylglutamic acid’/exp OR ‘pteroylglutamic acid’ OR ‘folvite’/exp OR ‘folvite’ OR ‘folacin’/exp OR ‘folacin’ OR ‘folate’/exp OR ‘folate’ OR ‘folic acid’/exp OR ‘folic acid’	59,344
#1	‘pregnancy’/exp OR ‘pregnant women’/exp OR ‘pregnancy’/de OR pregnant	648,650

543 results for search #11

9/8/14 EMBASE Benefits Addendum Search

No.	Query	Results
#7	#5 AND #6	0
#6	'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly'/exp OR exencephaly OR exencephalies	31,029
#5	#3 AND #4	11
#4	'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant	655,680
#3	#1 NOT #2	379
#2	'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements'	66,754
#1	'5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	1,429

3/24/15 EMBASE Benefits Search

No.	Query	Results
#11	#9 NOT #10	70
#10	#9 AND [medline]/lim	41
#9	#8 AND [2014-2015]/py	111
#8	#4 NOT #7	2,394
#7	#6 NOT #5	101
#6	#4 AND [animals]/lim	423
#5	#4 AND [humans]/lim	2,288
#4	#1 AND #2 AND #3	2,495
#3	'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly'/exp OR exencephaly OR exencephalies	31,662
#2	'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements' OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	69,216
#1	'pregnant women'/exp OR 'pregnant women' OR 'pregnancy'/exp OR 'pregnancy' OR pregnant	784,028

7/27/15 EMBASE Benefits Search

#9
#8 AND [24-10-2014]/sd NOT [27-7-2015]/sd
95

#8
#4 NOT #7
2,456

#7
#6 NOT #5
95

#6
#4 AND [animals]/lim
172

#5
#4 AND [humans]/lim
2,340

#4
#1 AND #2 AND #3
2,551

#3
'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly'/exp OR exencephaly OR exencephalies
32,319

#2
'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements' OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'
71,041

#1
'pregnant women'/exp OR 'pregnant women' OR 'pregnancy'/exp OR 'pregnancy' OR pregnant
802,358

11/18/15 EMBASE Benefits Search

#9
#8 AND [27-2-2015]/sd NOT [18-11-2015]/sd
108

#8
#4 NOT #7
2,500

#7
#6 NOT #5
97

#6
#4 AND [animals]/lim
176

#5
#4 AND [humans]/lim
2,384

#4
#1 AND #2 AND #3
2,597

#3
'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia' OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly' OR 'exencephaly'/exp OR exencephaly OR exencephalies
32,708

#2
'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements' OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate'/exp OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'
72,556

#1
'pregnant women'/exp OR 'pregnant women' OR 'pregnancy'/exp OR 'pregnancy' OR pregnant
816,404

1/28/16 EMBASE Benefits Search

#9
#8 AND [18-10-2015]/sd
23

#8
#4 NOT #7
2,512

#7
#6 NOT #5
98

#6
#4 AND [animals]/lim
177

#5
#4 AND [humans]/lim
2,396

#4
#1 AND #2 AND #3
2,610
Edit
Email alert
RSS feed

#3
'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia' OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly' OR 'exencephaly'/exp OR exencephaly OR exencephalies
32,949

#2
'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements' OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate'/exp OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'
73,279

#1
'pregnant women'/exp OR 'pregnant women' OR 'pregnancy'/exp OR 'pregnancy' OR pregnant

9/9/14 EMBASE Harms Search

Embase Session Results

No.	Query	Results
#11	#9 NOT #10	517
#10	#9 AND [medline]/lim	1,422
#9	#5 NOT #8	1,939
#8	#7 NOT #6	75
#7	#5 AND [animals]/lim	316
#6	#5 AND [humans]/lim	1,777
#5	#3 AND #4	2,014
#4	'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications	2,688,524
#3	#1 AND #2	6,768
#2	'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant	655,686
#1	'folic acid'/exp OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	49,006

11/11/14 EMBASE Harms Search

No.	Query	Results
#11	#9 NOT #10	128
#10	#9 AND [medline]/lim	100
#9	#8 AND [2013-2014]/py	228
#8	#4 NOT #7	2,362
#7	#6 NOT #5	97
#6	#4 AND [animals]/lim	420
#5	#4 AND [humans]/lim	2,257
#4	#1 AND #2 AND #3	2,459
#3	'spinal dysraphism'/exp OR 'spinal dysraphism' OR 'neural tube damage' OR 'neural tube defect'/exp OR 'neural tube defect' OR 'neural tube defects'/exp OR 'neural tube defects' OR 'neural tube disorders' OR 'neural tube defect, folate-sensitive' OR craniorachischisis OR craniorachischises OR 'diastematomyelia'/exp OR diastematomyelia OR diastematomyelias OR 'tethered cord syndrome'/exp OR 'tethered cord syndrome' OR 'tethered cord syndromes' OR 'occult spinal dysraphism sequence' OR 'tethered spinal cord syndrome' OR 'occult spinal dysraphism'/exp OR 'occult spinal dysraphism' OR 'occult spinal dysraphisms' OR 'iniencephaly'/exp OR iniencephaly OR iniencephalies OR 'neurenteric cyst' OR 'neurenteric cysts' OR 'neuroenteric cyst' OR 'neuroenteric cysts' OR 'spinal cord myelodysplasia' OR 'spinal cord myelodysplasias' OR acrania OR acranias OR 'exencephaly'/exp OR exencephaly OR exencephalies	31,173
#2	'vitamin b9' OR 'vitamin m'/exp OR 'vitamin m' OR 'pteroylglutamic acid'/exp OR 'pteroylglutamic acid' OR 'folvite'/exp OR 'folvite' OR 'folacin'/exp OR 'folacin' OR 'folate'/exp OR 'folate' OR 'folic acid'/exp OR 'folic acid' OR 'multivitamin'/exp OR multivitamin OR 'prenatal vitamin' OR 'multivitamins'/exp OR multivitamins OR 'prenatal vitamins' OR 'vitamin supplement' OR 'vitamin supplements' OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	67,655
#1	'pregnant women'/exp OR 'pregnant women' OR 'pregnancy'/exp OR 'pregnancy' OR pregnant	769,699

11/11/14 EMBASE Harms Search

No.	Query	Results
#12	#9 NOT #10 AND [2013-2014]/py	**142**
#11	#9 NOT #10	**522**
#10	#9 AND [medline]/lim	**1,431**
#9	#5 NOT #8	**1,953**
#8	#7 NOT #6	**75**
#7	#5 AND [animals]/lim	**320**
#6	#5 AND [humans]/lim	**1,791**
#5	#3 AND #4	**2,028**
#4	'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications	**2,711,985**
#3	#1 AND #2	**6,816**
#2	'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant	**660,630**
#1	'folic acid'/exp OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	**49,375**

3/24/15 EMBASE Harms Search

No.	Query	Results
#12	#9 NOT #10 AND [2014-2015]/py	77
#11	#9 NOT #10	551
#10	#9 AND [medline]/lim	1,446
#9	#5 NOT #8	1,997
#8	#7 NOT #6	76
#7	#5 AND [animals]/lim	328
#6	#5 AND [humans]/lim	1,835
#5	#3 AND #4	2,073
#4	'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications	2,778,112
#3	#1 AND #2	6,984
#2	'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant	673,619
#1	'folic acid'/exp OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	50,573

6/10/15 EMBASE Harms Addendum Search

No.	Query	Results
#12	#10 NOT #11	164
#11	#8 NOT #9 AND [medline]/lim	379
#10	#8 NOT #9	543
#9	'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications	2,826,063
#8	#5 OR #7	1,016
#7	#3 AND #6	949
#6	'adverse drug reaction'/exp OR 'adverse drug reaction'	1,320,972
#5	#3 AND #4	95
#4	'asthma' OR 'asthma'/exp OR asthma	238,789
#3	#1 AND #2	7,124
#2	'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant	682,899
#1	'folic acid'/exp OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'	51,450

164 results for search #12

7/27/15 EMBASE Harms Search

#12
#11 AND [6-7-2014]/sd NOT [27-7-2015]/sd
116

#11
#7 NOT #10
827

#10
#9 NOT #8
25

#9
#7 AND [animals]/lim
65

#8
#7 AND [humans]/lim
730

#7
#5 NOT #6
852

#6
#5 AND [medline]/lim
2,191

#5
#3 AND #4
3,043

#4
'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications OR 'twin pregnancy'/exp OR 'twins'/exp OR twin OR twins OR twinning OR 'asthma'/exp OR asthma
3,903,874

#3
#1 AND #2
7,683

#2
'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant
687,384

#1
'folic acid'/exp OR 'folic acid' OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate'/exp OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'

11/18/15 EMBASE Harms Search

95
#12
#11 AND [27-2-2015]/sd NOT [18-11-2015]/sd
853
#11
#7 NOT #10
25
#10
#9 NOT #8
65
#9
#7 AND [animals]/lim
755
#8
#7 AND [humans]/lim
878
#7
#5 NOT #6
2,210
#6
#5 AND [medline]/lim
3,088
#5
#3 AND #4
3,976,920
#4
'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications OR 'twin pregnancy'/exp OR 'twins'/exp OR twin OR twins OR twinning OR 'asthma'/exp OR asthma
7,857
#3
#1 AND #2
698,517
#2
'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant
59,181
#1
'folic acid'/exp OR 'folic acid' OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate'/exp OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'

1/28/16 EMBASE Harms Search

27
#12
#11 AND [18-10-2015]/sd
866
#11
#7 NOT #10
25
#10
#9 NOT #8
65
#9
#7 AND [animals]/lim
767
#8
#7 AND [humans]/lim
891
#7
#5 NOT #6
2,217
#6
#5 AND [medline]/lim
3,108
#5
#3 AND #4
4,017,311
#4
'colorectal tumor'/exp OR 'cyanocobalamin deficiency'/exp OR (b12 AND deficien*) OR 'pyridoxine deficiency'/exp OR (b6 AND deficien*) OR 'adverse drug reaction'/exp/mj OR 'patient harm'/exp/mj OR harm OR harms OR 'adverse drug reaction'/exp OR 'adverse drug reaction' OR 'adverse effect' OR 'adverse effects' OR 'adverse event' OR 'adverse events' OR complication OR complications OR 'twin pregnancy'/exp OR 'twins'/exp OR twin OR twins OR twinning OR 'asthma'/exp OR asthma
7,935
#3
#1 AND #2
705,446
#2
'pregnancy'/exp OR 'pregnant women'/exp OR 'pregnancy'/de OR pregnant
59,748
#1
'folic acid'/exp OR 'folic acid' OR 'folic acid':ti OR 'folic acid':ab OR folvite:ti OR folvite:ab OR folacin:ti OR folacin:ab OR '5 me thf' OR '5 me h4f' OR '5 methyltetrahydrofolate'/exp OR '5 methyltetrahydrofolate' OR '5 methyltetrahydropteroylpentaglutamate' OR '5-methyltetrahydrofolate triglutamate'

7/1/14 Gray Literature Benefits Search

ClinicalTrials.gov – 8
HSRProj (Health Services Research in Progress) – 5
Cochrane Library CENTRAL – no need to search separately, as this was included during the published literature search (there were 59 trials)

WHO ICTRP – searched the neural tube defect terms in the Condition box, and the folate terms in the intervention box, and found 7 trials
NIH RePORTER – used entire quoted search string and retrieved 15 grants

Websites:
NICHD – navigated to publications from the main page, and found and saves 3 pertinent folic acid documents. Also used the search box on the main site to search for "folic acid" and retrieved 45 other links to recent publications.

HRSA Maternal & Child Health Bureau – A search of "folic acid" yielded ~30 websites.

8/6/14 Gray Literature Harms Search

I. SPECIFIC HARMS
("folic acid" OR folvite OR folacin) AND ((twin OR twin OR twinning) OR "colorectal neoplasms" OR "colorectal cancer" OR "colorectal tumor" OR "vitamin b12 deficiency" OR "vitamin b6 deficiency") AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 421
HSRProj = 0
WHO ICTRP - put folate string in Title search and the other terms in Condition search = 45 records for 36 trials found.
NIH RePORTER - Advanced Search Logic - 2
HRSA Maternal and Child Health Bureau website - 6
NICHD - only small amount of text fits in search box. searched "folic acid" AND (harm* OR adverse*) - 10 results

II. GENERAL HARMS

("folic acid" OR folvite OR folacin) AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 1085
HSRProj = 0
WHO ICTRP = 1, duplicate with the specific search above, not saved.
NIH RePORTER - 30
HRSA Maternal and Child Health Bureau website - 21

3/27/15 Gray Literature Benefits Search

(Pregnancy OR pregnant OR "pregnant women") AND ("folic acid" OR "vitamin b9" OR "vitamin m" OR "Pteroylglutamic Acid" OR folvite OR folacin OR folate OR "folic acid" OR multivitamin OR "prenatal vitamin" OR multivitamins OR "prenatal vitamins" OR "vitamin supplement" OR "vitamin supplements" OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate) AND ("neural tube defects" OR "spina bifida" OR "neural tube damage" OR "neural tube defect" OR "neural tube disorders" OR Craniorachischisis OR Craniorachischises OR Diastematomyelia OR Diastematomyelias OR "Tethered Cord Syndrome" OR "Tethered Cord Syndromes" OR "Tethered Spinal Cord Syndrome" OR "Occult Spinal Dysraphism" OR "Occult Spinal Dysraphisms" OR Iniencephaly OR Iniencephalies OR "Neurenteric Cyst" OR "Neurenteric Cysts" OR "Neuroenteric Cyst" OR "Neuroenteric Cysts" OR "Spinal Cord Myelodysplasia" OR "Spinal Cord Myelodysplasias" OR Acrania OR Acranias OR Exencephaly OR Exencephalies)
ClinicalTrials.gov – 7 studies
HSRProj – 0
WHO ICTRP - searched the neural tube defect terms in the Condition box, and the folate terms in the intervention box, and found 2 trials
NIH RePORTER – Award notice date 7-1-14 or greater – 6 results

3/27/15 Gray Literature Harms Search

I. SPECIFIC HARMS

("folic acid" OR folvite OR folacin) AND ((twin OR twin OR twinning) OR "colorectal neoplasms" OR "colorectal cancer" OR "colorectal tumor" OR "vitamin b12 deficiency" OR "vitamin b6 deficiency") AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 105
HSRProj = 0
WHO ICTRP - put folate string in Title search and the other terms in Condition search = 5 records for 5 trials found.
NIH RePORTER - Advanced Search Logic - 1

II. GENERAL HARMS

("folic acid" OR folvite OR folacin) AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 280
HSRProj = 0
WHO ICTRP = 0
NIH RePORTER - 13

6/11/15 Gray Literature Addendum for Asthma

Previous gray literature searches already covered all needed adverse effects terms.
Search strategy:
("folic acid" OR folvite OR folacin) AND asthma
-ClinicalTrials.gov = 8
-HSRProj = 0
-WHO ICTRP (http://apps.who.int/trialsearch/AdvSearch.aspx) - put folate string in Title search and asthma in Condition search and search Recruitment status ALL = 56,
-NIH RePORTER (http://projectreporter.nih.gov/reporter.cfm) - Advanced Search Logic – 3
-HRSA Maternal and Child Health Bureau website (*mchb.**hrsa**.gov)* – 22
-Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) (https://www.nichd.nih.gov/Pages/index.aspx) - 0 results

7/28/15 Gray Literature Benefits Search

(Pregnancy OR pregnant OR "pregnant women") AND ("folic acid" OR "vitamin b9" OR "vitamin m" OR "Pteroylglutamic Acid" OR folvite OR folacin OR folate OR "folic acid" OR multivitamin OR "prenatal vitamin" OR multivitamins OR "prenatal vitamins" OR "vitamin supplement" OR "vitamin supplements" OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate) AND ("neural tube defects" OR "spina bifida" OR "neural tube damage" OR "neural tube defect" OR "neural tube disorders" OR Craniorachischisis OR Craniorachischises OR Diastematomyelia OR Diastematomyelias OR "Tethered Cord Syndrome" OR "Tethered Cord Syndromes" OR "Tethered Spinal Cord Syndrome" OR "Occult Spinal Dysraphism" OR "Occult Spinal Dysraphisms" OR Iniencephaly OR Iniencephalies OR "Neurenteric Cyst" OR "Neurenteric Cysts" OR "Neuroenteric Cyst" OR "Neuroenteric Cysts" OR "Spinal Cord Myelodysplasia" OR "Spinal Cord Myelodysplasias" OR Acrania OR Acranias OR Exencephaly OR Exencephalies)

ClinicalTrials.gov – 4 studies
HSRProj – 0 added to HSRProj in 2015
WHO ICTRP - searched the neural tube defect terms in the Condition box, and the folate terms in the intervention box, and found 0 trials.
NIH RePORTER – Award notice date 2-1-15 or greater– 10 results.

7/28/15 Gray Literature HARMS Search

I. SPECIFIC HARMS

("folic acid" OR folvite OR folacin) AND ((twin OR twin OR twinning) OR "colorectal neoplasms" OR "colorectal cancer" OR "colorectal tumor" OR "vitamin b12 deficiency" OR "vitamin b6 deficiency") AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications OR asthma)

ClinicalTrials.gov = 114
HSRProj = 0
WHO ICTRP - put all terms in title search = 0 records
NIH RePORTER - Advanced Search Logic - 0

II. GENERAL HARMS

(folic acid OR folvite OR folacin) AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 312
HSRProj = 0
WHO ICTRP = 0
NIH RePORTER - 19

11/18/15 Gray Literature Benefits Search

Benefits search strategy:
(Pregnancy OR pregnant OR "pregnant women") AND ("folic acid" OR "vitamin b9" OR "vitamin m" OR "Pteroylglutamic Acid" OR folvite OR folacin OR folate OR "folic acid" OR multivitamin OR "prenatal vitamin" OR multivitamins OR "prenatal vitamins" OR "vitamin supplement" OR "vitamin supplements" OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate) AND ("neural tube defects" OR "spina bifida" OR "neural tube damage" OR "neural tube defect" OR "neural tube disorders" OR Craniorachischisis OR Craniorachischises OR Diastematomyelia OR Diastematomyelias OR "Tethered Cord Syndrome" OR "Tethered Cord Syndromes" OR "Tethered Spinal Cord Syndrome" OR "Occult Spinal Dysraphism" OR "Occult Spinal Dysraphisms" OR Iniencephaly OR Iniencephalies OR "Neurenteric Cyst" OR "Neurenteric Cysts" OR "Neuroenteric Cyst" OR "Neuroenteric Cysts" OR "Spinal Cord Myelodysplasia" OR "Spinal Cord Myelodysplasias" OR Acrania OR Acranias OR Exencephaly OR Exencephalies)

ClinicalTrials.gov – 2 studies
HSRProj – 0
WHO ICTRP - searched the neural tube defect terms in the Condition box, and the folate terms in the intervention box, and found 0 trials.
NIH RePORTER – Advanced Text search logic/ Award notice date 7-1-15 or greater – 11 results.

11/18/15 Gray Literature HARMS Search

I. SPECIFIC HARMS

("folic acid" OR folvite OR folacin) AND ((twin OR twin OR twinning) OR "colorectal neoplasms" OR "colorectal cancer" OR "colorectal tumor" OR "vitamin b12 deficiency" OR "vitamin b6 deficiency") AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications OR asthma)

ClinicalTrials.gov = 90
HSRProj = 0
WHO ICTRP - put all terms in title search = 0 records
NIH RePORTER - Advanced Search Logic – 1 record

II. GENERAL HARMS

(folic acid OR folvite OR folacin) AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 268
HSRProj = 0
WHO ICTRP = 0
NIH RePORTER - 12

2/1/16 Gray Literature Benefits Search

Benefits search strategy:
(Pregnancy OR pregnant OR "pregnant women") AND ("folic acid" OR "vitamin b9" OR "vitamin m" OR "Pteroylglutamic Acid" OR folvite OR folacin OR folate OR "folic acid" OR multivitamin OR "prenatal vitamin" OR multivitamins OR "prenatal vitamins" OR "vitamin supplement" OR "vitamin supplements" OR 5-Me-THF OR 5-Me-H4F OR 5-methyltetrahydrofolate) AND ("neural tube defects" OR "spina bifida" OR "neural tube damage" OR "neural tube defect" OR "neural tube disorders" OR Craniorachischisis OR Craniorachischises OR Diastematomyelia OR Diastematomyelias OR "Tethered Cord Syndrome" OR "Tethered Cord Syndromes" OR "Tethered Spinal Cord Syndrome" OR "Occult Spinal Dysraphism" OR "Occult Spinal Dysraphisms" OR Iniencephaly OR Iniencephalies OR "Neurenteric Cyst" OR "Neurenteric Cysts" OR "Neuroenteric Cyst" OR "Neuroenteric Cysts" OR "Spinal Cord Myelodysplasia" OR "Spinal Cord Myelodysplasias" OR Acrania OR Acranias OR Exencephaly OR Exencephalies)

ClinicalTrials.gov – 0 studies
HSRProj – 0
WHO ICTRP - 0
NIH RePORTER – 1
Advanced Text search logic/ Award notice date 10-18-15 or greater – 1 result.

2/1/16 Gray Literature HARMS Search

I. SPECIFIC HARMS

("folic acid" OR folvite OR folacin) AND ((twin OR twin OR twinning) OR "colorectal neoplasms" OR "colorectal cancer" OR "colorectal tumor" OR "vitamin b12 deficiency" OR "vitamin b6 deficiency") AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications OR asthma)

ClinicalTrials.gov = 73
HSRProj = 0
WHO ICTRP - put all terms in title search = 0 records
NIH RePORTER - Advanced Search Logic – 0 records

II. GENERAL HARMS

(folic acid OR folvite OR folacin) AND ("drug-related side effects" OR "adverse reaction" OR harm OR harms OR "adverse effect" OR "adverse effects" OR "adverse event" OR "adverse events" OR Complication OR Complications)

ClinicalTrials.gov = 245
HSRProj = 0
WHO ICTRP = 0
NIH RePORTER - 3

Appendix B. Inclusion/Exclusion Criteria

	Include	Exclude
Populations	KQ 1: Women of childbearing age (postmenarchal and premenopausal; women with the potential for or planning childbearing) KQ 2: Women of childbearing age (postmenarchal and premenopausal; women with the potential for or planning childbearing); fetus, neonate, or child from index pregnancy	KQ 1: Prepubertal girls; men; women without the potential for childbearing (e.g., women who are postmenopausal or have genetic uterine or ovarian abnormalities)
Interventions	Folic acid supplementation, with or without food fortification or naturally occurring folate, for the prevention of neural tube defects and other birth defects Supplementation with micronutrients (e.g., multivitamins, iron) in combination with folic acid for the prevention of neural tube defects only	Food fortification only Naturally occurring folate only Counseling to improve dietary supplementation Supplementation with micronutrients (e.g., multivitamins, iron) in combination with folic acid for the prevention of harms only
Comparisons	KQs 1a, 1b, 2a: Placebo or no treatment; dietary supplementation only; supplementation with prenatal vitamins without folic acid; iron supplements without folic acid KQs 1b, 1c, 2b: All of the above plus folic acid supplementation of varying dosages	KQs 1a, 1b, 2a: Lower or higher doses of folic acid supplementation; folic acid vs. other active comparators KQs 1c, 2b: Folic acid vs. other active comparators (e.g., multivitamins)
Outcomes	Neonatal outcomes: Neural tube defects Harms from treatment: Twins Colorectal cancer or other reported types of cancer Vitamin B12 deficiency Vitamin B6 deficiency Other reported child, neonatal, fetal, or maternal harms	Benefits not specified in inclusion criteria
Timing	KQs 1a, 1b: Supplementation initiated before index pregnancy or in the first trimester KQs 1c, 2a, 2b: All timing	KQs 1a, 1b: Supplementation initiated after the first trimester of pregnancy
Settings	Developed countries categorized as “Very High” on the Human Development Index (as defined by the United Nations Development Programme)	Countries not categorized as “Very High” on the Human Development Index
Study designs	Efficacy (KQ 1): Randomized, controlled trials; controlled clinical trials; cohort or case-control studies Harms (KQ 2): Randomized, controlled trials; controlled clinical trials; or observational studies (case-control, cohort, registry data)	Commentaries, editorials, case reports
Sample size	More than 50 participants	50 participants or less
Quality	Good and fair quality	Poor quality
Language	English	Non-English studies

Appendix C: Excluded Studies

X 1 Wrong publication type (Editorials, Letters, Opinions, or Commentaries to the editor with no primary data, Nonsystematic Review articles)

X 2 Wrong population (Populations were not women of childbearing age [e.g., pre-menarchy, post-menopausal, no potential for childbearing)

X 3 Wrong or no comparator (Single group design with no comparator; Active comparator [e.g., head-to-head trial])

X 4 Wrong or no outcome (See Include/Exclude criteria for exceptions)

X 5 Wrong timing (supplementation initiated after the first trimester for benefits only)

X 6 Wrong geographical setting (Countries with human development index of low to high)

X 7 Wrong Study Design (Case reports, case series, cross-sectional designs)

X 8 Wrong or no intervention (As defined in the Include/Exclude criteria)

X 9 Study size <50 subjects

X 10 Wrong language (non-English)

X 11 Full-text irretrievable

1. Folic acid and combined iron and folic acid preparations. Br Med J. 1968 Oct 12;4(5623):102-3. PMID: 5696538. Exclusion Code: X 1
2. Folates and the fetus. Lancet. 1977 Feb 26;1(8009):462. PMID: 65568. Exclusion Code: X 1
3. Trial of folate treatment to prevent recurrence of neural tube defects. Br Med J (Clin Res Ed). 1981 May 30;282(6278):1793. PMID: 6786625. Exclusion Code: X 1
4. Vitamin supplements to prevent neural tube defects. Lancet. 1982 May 8;1(8280):1075. PMID: 6122879. Exclusion Code: X 1
5. Vitamins during pregnancy and neural tube defects. JAMA. 1990 May 23-30;263(20):2747-9. PMID: 2332916. Exclusion Code: X 1
6. Periconceptional use of multivitamins and the prevalence of neural-tube defects. N Engl J Med. 1990 Apr 12;322(15):1082-4. PMID: 2320071. Exclusion Code: X 1
7. Vitamins to prevent neural tube defects. Lancet. 1991 Oct 5;338(8771):894-5. PMID: 1681257. Exclusion Code: X 1
8. From the Centers for Disease Control. Use of folic acid for prevention of spina bifida and other neural tube defects--1983-1991. JAMA. 1991 Sep 4;266(9):1190-1. PMID: 1870237. Exclusion Code: X 1
9. Folic acid to prevent neural tube defects. Lancet. 1991 Aug 24;338(8765):505-6. PMID: 1678457. Exclusion Code: X 1
10. Folic acid and neural tube defects. Lancet. 1991 Jul 20;338(8760):153-4. PMID: 1677069. Exclusion Code: X 1
11. Folic acid in the prevention of neural tube defects. Geneesmiddelenbulletin. 1991;25(12):56. Exclusion Code: X 1
12. CDC report: Folic acid and pregnancy. Am Fam Physician. 1992;46(6):1842. Exclusion Code: X 1
13. Periodic health examination, 1994 update: 3. Primary and secondary prevention of neural tube defects. Canadian Task Force on the Periodic Health Examination. CMAJ. 1994 Jul 15;151(2):159-66. PMID: 7518734. Exclusion Code: X 1
14. Folic acid fortification. Nutr Rev. 1996 Mar;54(3):94-5. PMID: 8935221. Exclusion Code: X 1
15. Folic acid. Can Pharm J. 1997;130(9):28. Exclusion Code: X 1

16. Low-dosage folic acid reduces the incidence of neural tube defects. Drugs and Therapy Perspectives. 1997;10(2):10-1. Exclusion Code: X 1

17. Folate delivers head-to-toe health advantages. The B vitamin that benefits unborn babies may also protect the hearts and minds (and colons) of adults. Health News. 2002 Dec;8(12):1-2. PMID: 12523265. Exclusion Code: X 1

18. Folic acid supplementation to prevent neural tube defects. Med Lett Drugs Ther. 2004 Mar 1;46(1177):17-8. PMID: 15041889. Exclusion Code: X 1

19. Folate and vitamin B12 deficiencies: proceedings of a WHO technical consultation held 18-21 October, 2005, in Geneva, Switzerland. Introduction. Food Nutr Bull. 2008 Jun;29(2 Suppl):S3-4. PMID: 18709877. Exclusion Code: X 1

20. Cochrane Pregnancy and Childbirth Group. About The Cochrane Collaboration: John Wiley & Sons, Ltd; 2015. Exclusion Code: X 1

21. Abramsky L, Noble J. Effects of folic acid. Lancet. 2002 Jun 8;359(9322):2039-40. PMID: 12076582. Exclusion Code: X 1

22. Al-Mendalawi MD. Towards a national program to combat neural tube defects in Iraq. Congenital Anomalies. 2014;54(2):123. Exclusion Code: X 1

23. Althaus F. Folic acid supplementation during early pregnancy appears to lessen risk of neural tube defects. Fam Plann Perspect. 1990;22(3):140-1. Exclusion Code: X 1

24. Banhidy F, Czeizel AE. Primary prevention of congenital abnormalities with specified origin. Clin Chem Lab Med. 2012;50(2):A65-A6. Exclusion Code: X 1

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Appendix D. Risk of Bias Assessments for All Included Studies

Table D-1. Risk of bias assessments for all included systematic reviews and meta-analyses (Part 1)

First Author, Year	Comprehensive literature search performed?	Was the status of publication used as an inclusion criterion?	Was an 'a priori' design provided?	Was a list of studies provided?	Was there explicit inclusion/exclusion criteria for the selection of studies?	Were the characteristics of the included studies provided?	Was the likelihood of publication bias assessed?	Was there duplicate study selection and data extraction?
Brown et al., 2014[137]	No	Unclear	No	No	No	Yes	No	Unclear
Crider et al, 2013[94]	Yes	No	Unclear	No	Yes	Yes	Yes	Yes
Goh et al., 2006[77]	Yes	No	No	No	No	No	Yes	Yes
Wolff et al., 2009[32] Wolff et al., 2009[79]	Yes	Unclear	Yes	Yes	Yes	Yes	No	Yes
Yang et al., 2014[101]	Yes	No	Unclear	No	Yes	Yes	Yes	Unclear

Table D-2. Risk of bias assessments for all included systematic reviews and meta-analyses (Part 2)

First Author, Year	Was the scientific quality of the included studies assessed and documented?	Was the conflict of interest included?	Was the scientific quality of the included studies used appropriately in formulating conclusions?	Were the methods used to combine the findings of studies appropriate?	Was the authors' conclusions supported by the evidence they presented?	Risk of Bias Rating	Comments
Brown et al., 2014[137]	No	No	NA	Unclear	No	High	Although the review is titled a systematic review, details NR regarding all crucial aspects of systematic review such as searches, review, risk of bias appraisal, synthesis, and so on.
Crider et al, 2013[94]	Yes	Unclear	Yes	Yes	Yes	Low	
Goh et al., 2006[77]	No	No	No	Yes	Yes	High	Not assess quality. Characteristics of studies included in the meta-analysis were not presented; Appropriate synthesis and statistical testing, but no discussion of publication bias.
Wolff et al., 2009[32] Wolff et al., 2009[79]	Yes	no	Yes	NA	Yes	Low	
Yang et al., 2014[101]	Yes	Unclear	Unclear	Yes	Yes	Medium	Unclear how authors used risk of bias assessments in the analysis. The study noted that they included high quality studies)

NA = not applicable

Low: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions.

Medium: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies.

High: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies.

Table D-3. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 1)

First Author, Year	Were eligibility criteria described clearly?	Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented across all study participants?	Was the symptom status of subjects determined using valid and reliable methods, implemented across all study participant?	Was the intervention or exposure clearly defined, across all study participant?	Was method of randomization adequate?	Was allocation concealment adequate?
Abe et al., 2014[138]	No	Unclear	NA	Unclear	NA	NA
Abe et al., 2013[139]	No	Unclear	NA	No	NA	NA
Abe et al., 2015[140]	No	Unclear	NA	Unclear	NA	NA
Agopian et al., 2013[9]	Yes	Yes	Yes	No	NA	NA
Ahrens et al., 2011[11]	Yes	Yes	Unclear	Yes	NA	NA
Berry et al., 2004[141]	Yes	Yes	Yes	No	NA	NA
Botto et al., 2002[142]	Yes	Yes	Yes	Yes	NA	NA
Bower et al., 1989[143] Bower, 1992[144]	Yes	Yes	Yes	No	NA	NA
Brescianini et al., 2012[145]	No	Unclear	Yes	Unclear	NA	NA
Carmichael et al., 2010[146]	Yes	Yes	Yes	No	NA	NA
Chandler et al., 2012[147]	Yes	Yes	Yes	No	NA	NA
Charles et al., 2004[148] Charles et al., 2005[149] Taylor et al., 2015[150]	Yes	Yes	Yes	Yes	No	Yes
Correa et al., 2012[114]	Yes	Yes	Yes	No	NA	NA
Czeizel et al., 2004[151]	Yes	Yes	Yes	Yes	NA	NA
Czeizel et al., 2004[74]	Yes	Yes	NA	Yes	NA	NA
Czeizel et al., 1992[81]; Czeizel et al., 1993[85]	Yes	Yes	NA	Yes	Yes	Unclear
Czeizel et al., 1996[152]	Yes	Yes	Yes	Yes	NA	NA
Czeizel et al., 2004[74]	Yes	Yes	NA	Yes	NA	NA
Czeizel et al., 2004[151]	Yes	Yes	Yes	Yes	NA	NA
De Marco et al., 2011[153]	Yes	Yes	Yes	Yes	NA	NA

Table D-3. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 1) (continued)

First Author, Year	Were eligibility criteria described clearly?	Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented across all study participants?	Was the symptom status of subjects determined using valid and reliable methods, implemented across all study participant?	Was the intervention or exposure clearly defined, across all study participant?	Was method of randomization adequate?	Was allocation concealment adequate?
DeSoto et al., 2012[154]	Yes	Yes	Yes	No	NA	NA
Ericson et al., 2001[155]	No	No	NA	No	NA	NA
Gildestad et al., 2013[156]	Unclear	Unclear	Unclear	Unclear	NA	NA
Haberg et al., 1994[157]	Unclear	Unclear	NA	Unclear	NA	NA
Hernandez et al., 2001[88]	Yes	Yes	Yes	Unclear	NA	NA
Kallen et al., 2004[158]	Yes	Yes	Yes	No	NA	NA
Kallen et al., 2007[159]	Yes	Yes	NA	No	NA	NA
Kondo et al., 2015[160]	No	Yes	Unclear	No	NA	NA
Medvezky et al., 2003[161]	Yes	Yes	Yes	No	NA	NA
Mills et al., 1989[89]	No	Yes	Yes	Yes	NA	NA
Moore et al., 2003[91] Milunsky et al., 1989[90]	Yes	Yes	NA	Yes	NA	NA
Mosley et al.,[80]	Yes	Yes	Yes	Yes	NA	NA
Mulinare et al., 1988[162]	Yes	Yes	Yes	Yes	NA	NA
Ohya et al., 2011[163]	No	Unclear	NA	Unclear	NA	NA
Shaw et al., 2002[164]	Yes	Yes	Yes	No	NA	NA
Shaw et al., 1995[75]	Yes	Yes	Yes	Yes	NA	NA
Suarez et al., 2000[20]	Yes	Yes	Unclear	Yes	NA	NA
Veeranki et al., 2014[165]	Yes	Yes	NA	No	NA	NA
Veeranki et al., 2014[166]	No	Unclear	NA	No	NA	NA
Veeranki et al., 2015[167]	Yes	Yes	NA	No	NA	NA
Vollset et al., 2005[76]	Yes	Yes	Yes	No	NA	NA
Werler et al., 1993[92]	Yes	Unclear	Yes	Yes	NA	NA

NA = not applicable

Table D4. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 2)

First Author, Year	Was the strategy for recruiting participants into the study the same across study groups?	Do start of follow-up and start of intervention coincide?	Are baseline characteristics similar between groups?	Did the study control for baseline differences between groups?	Were the participants and the administrators of the intervention blinded to the intervention or exposure status of participants?	Were the outcome assessors blinded to the outcome status of participants?
Abe et al., 2014[138]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Abe et al., 2013[139]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Abe et al., 2015[140]	Unclear	Unclear	Unclear	Unclear	No	Unclear
Agopian et al., 2013[9]	No	NA	No	Yes	NA	NA
Ahrens et al., 2011[11]	Unclear	NA	No	Yes	NA	NA
Berry et al., 2004[141]	NA (registry)	No	Unclear	Unclear	NA	Unclear
Botto et al., 2002[142]	No	NA	Yes	Yes	NA	Yes
Bower et al., 1989[143] Bower et al., 1992[144]	No	NA	Unclear	Unclear	NA	NA
Brescianini et al., 2012[145]	Unclear	No	Unclear	Unclear	NA	NA
Carmichael et al., 2010[146]	Yes	NA	No	Yes	NA	NA
Chandler et al., 2012[147]	No	NA	No	Yes	NA	NA
Charles et al., 2004[148] Charles et al., 2005[149] Taylor et al., 2015[150]	NA	NA	No	Yes	No	Unclear
Correa et al., 2012[114]	No	NA	No	Yes	NA	NA
Czeizel et al., 2004[151]	Yes	No	No	No	NA	NA
Czeizel et al., 2004[74]	No	no	No	Yes	No	Unclear
Czeizel et al., 1992[81]; Czeizel et al., 1993[85]	NA	Yes	Yes	NA	Unclear	Unclear
Czeizel et al., 1996[152]	Yes	No	Unclear	Unclear	NA	NA
Czeizel et al., 2004[74]	No	No	No	Yes	No	Unclear
Czeizel et al., 2004[151]	Yes	No	No	No	NA	NA
De Marco et al., 2011[153]	Yes	NA	No	Yes	NA	NA
DeSoto et al., 2012[154]	Yes	NA	Yes	Yes	NA	NA
Ericson et al., 2001[155]	Unclear	No	Unclear	Unclear	Unclear	Unclear
Gildestad et al., 2013[156]	Unclear	No	Unclear	Unclear	Unclear	Unclear
Haberg et al., 1994[157]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Hernandez et al., 2001[88]	Yes	NA	No	Yes	NA	Unclear
Kallen et al., 2004[158]	NA (registry)	No	Unclear	Unclear	NA	Unclear
Kallen et al., 2007[159]	Yes	No	No	Yes	Unclear	Unclear
Kondo et al., 2015[160]	No	NA	No	Yes	NA	NA

Table D4. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 2) (continued)

First Author, Year	Was the strategy for recruiting participants into the study the same across study groups?	Do start of follow-up and start of intervention coincide?	Are baseline characteristics similar between groups?	Did the study control for baseline differences between groups?	Were the participants and the administrators of the intervention blinded to the intervention or exposure status of participants?	Were the outcome assessors blinded to the outcome status of participants?
Medvezky et al., 2003[161]	Yes	NA	Unclear	Unclear	NA	NA
Mills et al., 1989[89]	No	NA	No	Yes	NA	Unclear
Moore et al., 2003[91] Milunsky et al., 1989[90]	Yes	No	No	Yes	No	No
Mosley et al., 1988[80]	Yes	NA	Yes	Yes	NA	Unclear
Mulinare et al., 1988[162]	No	NA	Unclear	Unclear	NA	Unclear
Ohya et al., 2011[163]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Shaw et al., 2002[164]	No	NA	Unclear	Unclear	NA	NA
Shaw et al., 1995[75]	No	NA	No	Yes	NA	NA
Suarez et al., 2000[20]	No	NA	Unclear	Yes	NA	NA
Veeranki et al., 2014[165]	Yes	No	No	Yes	Unclear	Unclear
Veeranki et al., 2014[166]	Yes	No	Unclear	Unclear	No	Unclear
Veeranki et al., 2015[167]	Yes	No	No	Yes	No	Yes
Vollset et al., 2005[76]	Yes	Unclear	Unclear	Yes	Unclear	Unclear
Werler et al., 1993[92]	Unclear	Yes	Unclear	No	NA	NA

NA= not applicable

Table D5. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 3)

First Author, Year	Were outcome assessors blinded to the exposure?	Was intervention fidelity adequate?	Was there a risk of recall bias?	Did the study focus on the time period that we are interested in?	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Did variation from the study protocol compromise the conclusions of the study?
Abe et al., 2014[138]	NA	Unclear	Unclear	Unclear	Unclear	Unclear
Abe et al., 2013[139]	NA	Unclear	Yes	Unclear	No	NA
Abe et al., 2015[140]	NA	Unclear	Yes	Yes	Unclear	NA
Agopian et al., 2013[9]	Unclear	Unclear	Unclear	Yes	Yes	NA
Ahrens et al., 2011[11]	Yes	Unclear	Unclear	Yes	Yes	NA
Berry et al., 2004[141]	NA	Unclear	Unclear	No	No	NA
Botto et al., 2002[142]	Unclear	Yes	Unclear	Yes	Yes	NA
Bower et al., 1989[143] Bower et al., 1992[144]	Unclear	Unclear	Unclear	Unclear	Yes	NA
Brescianini et al., 2012[145]	Unclear	Unclear	Unclear	Unclear	No	NA
Carmichael et al., 2010[146]	Unclear	Unclear	Unclear	No	Yes	NA
Chandler et al., 2012[147]	Unclear	Unclear	Yes	Yes	Yes	NA
Charles et al., 2004[148] Charles et al., 2005[149] Taylor et al., 2015[150]	NA	Yes	No	Yes	No	No
Correa et al., 2012[114]	Unclear	Unclear	Yes	No	No	NA
Czeizel et al., 2004[151]	Unclear	Unclear	Unclear	Unclear	No	NA
Czeizel et al., 2004[74]	Unclear	Unclear	No	Yes	No	No
Czeizel et al., 1992[81]; Czeizel et al., 1993[85]	NA	Yes	No	Yes	No	No
Czeizel et al., 1996[152]	Unclear	Unclear	Unclear	Yes	No	NA
Czeizel et al., 2004[74]	Unclear	Unclear	No	Yes	No	No
Czeizel et al., 2004[151]	Unclear	Unclear	Unclear	Unclear	No	NA
De Marco et al., 2011[153]	Unclear	Yes	Unclear	No	No	NA
DeSoto et al., 2012[154]	Unclear	Unclear	Yes	No	No	NA
Ericson et al., 2001[155]	NA	Yes	Unclear	Unclear	No	NA
Gildestad et al., 2013[156]	NA	Unclear	Unclear	Unclear	No	NA
Haberg, 1994[157]	NA	Unclear	Unclear	Yes	Unclear	NA
Hernandez et al., 2001[88]	Unclear	Yes	Unclear	No	No	NA
Kallen et al., 2004[158]	NA	Unclear	Unclear	No	No	NA
Kallen et al., 2007[159]	NA	Yes	Unclear	Unclear	No	NA

Table D5. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 3) (continued)

First Author, Year	Were outcome assessors blinded to the exposure?	Was intervention fidelity adequate?	Was there a risk of recall bias?	Did the study focus on the time period that we are interested in?	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?	Did variation from the study protocol compromise the conclusions of the study?
Kondo et al., 2015[160]	No	Unclear	Yes	Unclear	No	NA
Medvezky et al., 2003[161]	Unclear	Unclear	Unclear	No	Unclear	NA
Mills et al., 1989[89]	Yes	Yes	Unclear	Yes	Yes	NA
Moore et al., 2003[91] Milunsky et al., 1989[90]	NA	Unclear	Unclear	No	Yes	NA
Mosley et al., 2009[80]	Unclear	Yes	Unclear	Yes	Yes	NA
Mulinare et al., 1988[162]	Yes	Unclear	Yes	No	No	NA
Ohya et al., 2011[163]	NA	Unclear	Unclear	Unclear	Unclear	Unclear
Shaw et al., 2002[164]	Unclear	Unclear	Yes	No	Yes	NA
Shaw et al., 1995[75]	Yes	Unclear	Unclear	Yes	Yes	NA
Suarez et al., 2000[20]	Unclear	Yes	Unclear	Yes	Unclear	NA
Veeranki et al., 2014[165]	NA	Unclear	No	Unclear	No	NA
Veeranki et al., 2014[166]	NA	Unclear	No	Yes	No	NA
Veeranki et al., 2015[167]	NA	Unclear	No	Unclear	No	NA
Vollset et al., 2005[76]	NA	Unclear	No	Unclear	No	NA
Werler et al., 1993[92]	Unclear	Yes	Yes	Yes	Yes	NA

NA = not applicable

Table D6. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 4)

First Author, Year	What was the overall attrition/overall response rate?	What was the overall differential attrition?	Did the study have high attrition or low response rate raising concern for bias?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Did the analysis adjust for potential confounders?	Did the study have cross-overs or contamination raising concern for bias?
Abe et al., 2014[138]	Unclear	Unclear	Unclear	Na	Unclear	Unclear
Abe et al., 2013[139]	Unclear	Unclear	Unclear	NA	Unclear	Unclear
Abe et al., 2015[140]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Agopian et al., 2013[9]	Response Rate (overall sample in original study; see Yoon et al., 2001 companion article) G1 + G2: About 74 (NR out of 7,470) G2: About 63 (NR out of 3,821)	NA	Unclear	NA	Unclear	NA
Ahrens et al., 2011[11]	G1: 66% G2: 53%	NA	no	NA	Yes	NA
Berry et al., 2004[141]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Botto et al,, 2002[142]	Overall sample G1: 69% G2: 71% NTD analysis G1: NR G2: NR	NA	Unclear	NA	Unclear	NA
Bower et al., 1989[143] Bower et al., 1992[144]	G1: 93% G2: 88% G3: 84%	Response Rate G1: 93 (77/83) G2: 88 (77/87) G3: 84 (154/183)	No	NA	No	NA
Brescianini et al., 2012[145]	G1: 93% G2: 88% G3: 84%	NA	No	NA	No	NA
Carmichael et al., 2010[146]	G1: 73 (146/200) G2: 79 (191/241) G3: 80% (626/786)	NA	No	NA	Yes	NA
Chandler et al., 2012[147]	62% for anencephaly; 76% spina bifida and 71% controls	NA	No	NA	Unclear	NA

Table D6. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 4) (continued)

First Author, Year	What was the overall attrition/overall response rate?	What was the overall differential attrition?	Did the study have high attrition or low response rate raising concern for bias?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Did the analysis adjust for potential confounders?	Did the study have cross-overs or contamination raising concern for bias?
Charles et al., 2004[148] Charles et al., 2005[149] Taylor et al., 2015 [150]	Unclear	Unclear	Unclear	No	NA	No
Correa et al., 2012[114]	Overall, 70% among mothers of case infants and 67% among mothers of control infants. Response rate not reported for NTD mothers	NA	Unclear	NA	Yes	NA
Czeizel et al., 2004[151]	Unclear	NA	Unclear	NA	Yes	NA
Czeizel et al., 2004[74]	Overall attrition Unclear	G1: 3069/3981 (77.1%) G2: Unclear	Yes	No	Yes	Unclear
Czeizel et al., 1992[81]; Czeizel et al., 1993[85]	1%	0.10%	No	NA	NA	No
Czeizel et al., 1996[152]	63% for negative controls, rate for positive controls NR	NA	Unclear	Na	No	NA
Czeizel et al., 2004[74]	Overall attrition Unclear	G1: 3069/3981 (77.1%) G2: Unclear	Yes	No	Yes	Unclear
Czeizel et al., 2004[151]	Unclear	NA	Unclear	NA	Unclear	NA
De Marco et al., 2011[153]	Response Rate G1: 92 (133/145) G2: 82 (273/332)	NA	No	NA	Unclear	NA
DeSoto et al., 2012[154]	Response Rate G1: 48.1% (321/668) G2: 31.7% (774/2444)	NA	Yes	NA	Unclear	NA
Ericson et al., 2001[155]	Unclear	Unclear	Unclear	NA	Yes	No
Gildestad et al., 2013[156]	Unclear	NA	Unclear	NA	Unclear	Unclear
Haberg et al., 1994[157]	Unclear	Unclear	NA	Unclear	Unclear	Unclear

Table D6. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 4) (continued)

First Author, Year	What was the overall attrition/overall response rate?	What was the overall differential attrition?	Did the study have high attrition or low response rate raising concern for bias?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Did the analysis adjust for potential confounders?	Did the study have cross-overs or contamination raising concern for bias?
Hernandez et al., 2001[88]	Response Rate G1: 84% (1,242/NR) G2: 83% (6,600/NR) G3: 80% (1,626/NR) G4: NR (2,138/NR)	NA	No	NA	No	NA
Kallen et al., 2004[158]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Kallen et al., 2007[159]	Unknown	Unclear	Unclear	NA	Yes	No
Kondo et al., 2015[160]	Response Rate G1: 79% G2: 56%	NA	No	NA	Yes	NA
Medvezky et al., 2003[161]	96.9% cases; 96% other non-NTD cases; 83.1% controls	NA	Yes (was Unclear)	NA	Unclear	NA
Mills et al., 1989[89]	Response Rate G1: 64.8%-82% (571/NR) G2: NR (546/NR) G3: NR (573/NR)	NA	No	NA	Unclear	NA
Moore et al., 2003[91] Milunsky et al., 1989[90]	3% (715/23,491)	Unclear	No	NA	Unclear	No
Mosley et al., 2009[80]	62% anencephaly; 76% SB; 71% controls	NA	No	NA	Yes	NA
Mulinare, 1988[162]	G1: 347/519 (66.9%) G2: 2829/4043 (69.9%)	NA	No	NA	Yes	NA
Ohya et al., 2011[163]	Unclear	Unclear	Unclear	NA	Unclear	Unclear
Shaw et al., 2002[164]	Response Rate G1 (NTD only): 84% G2: 76% from both control cohorts	NA	No	NA	No	NA
Shaw et al., 1995[75]	88% both groups	NA	No	NA	Yes	NA
Suarez et al., 2000[20]	72% cases; 53% controls	NA	No	NA	Yes	NA
Veeranki et al., 2014[165]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Veeranki et al., 2014[166]	Unclear	Unclear	Unclear	NA	Yes	Unclear

Table D6. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 4) (continued)

First Author, Year	What was the overall attrition/overall response rate?	What was the overall differential attrition?	Did the study have high attrition or low response rate raising concern for bias?	Is the analysis conducted on an intention-to-treat (ITT) basis?	Did the analysis adjust for potential confounders?	Did the study have cross-overs or contamination raising concern for bias?
Veeranki et al., 2015[167]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Vollset et al., 2005[76]	Unclear	Unclear	Unclear	NA	Yes	Unclear
Werler et al., 1993[92]	G1: 567-436/567=76.9% G2: 3672-2615/3672=71.2%	NA	No	NA	Yes	NA

G1 = group 1; G2 = group 2; G3 = group 3; G4 = group 4; ITT = intent to treat; NA = not applicable; NR = not reported; NTD = neutral tube defect

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Abe et al., 2014[138]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Not enough information in publication to judge risk of bias
Abe et al., 2013[139]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Meeting abstract with very little information to base judgment
Abe et al., 2015[140]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Study does not provide sufficient detail to evaluate ROB
Agopian et al., 2013[9]	Yes	NA	NA	NA	Unclear	Medium	Most of the major important confounders were adjusted for in the analyses. However, still a possibility of residual confounding because some NTD-specific variables not controlled for, specifically, previous NTD pregnancy or having or having partner(s) with NTDs. Cases and controls selected from different populations. Specifically, cases could be stillborn infants or therapeutic abortions, while all controls were liveborn infants. Definition of exposure not defined clearly. Positive response to folic acid supplement use question could have indicated any frequency of usage.
Ahrens et al., 2011[11]	Yes	NA	NA	NA	Unclear	Medium	Ascertainment of cases for non-live births is not routine; Unclear how missing data was handled (although “all women were included” in the analysis)

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Berry et al., 2004[141]	Yes	Yes	Yes	Yes	Unclear	High	The study itself does not describe the data source well, but it cites other studies that do. Based on these other studies, we infer that the exposure period starts before pregnancy and extends to first attendance (in 90% of cases before the end of the first trimester and usually around week 10) with lack of clarity on degree of exposure, difficult to clearly distinguish exposure from non-exposure; authors did not specify definition of exposure clearly (defined as any vs. no supplement), so the degree of adherence to MV is Unclear; although study does not appear to account for fetal deaths, the resulting selection bias would serve to mute rather than exaggerate the effect of FA on twinning; study uses probabilistic simulations to assess bias caused by misclassification of the use of IVF.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Botto, 2002[142]	Yes	NA	NA	NA	Unclear	High	Cases and controls selected from different populations. Cases could be liveborn or stillborn infants, while all controls were liveborn infants. No information about 1) timing of data collection given to assess recall bias; 2) whether potential NTD-specific confounders measured or adjusted for in analyses; 3) exposure to dietary folate; 4) response rates for patients analyzed for analysis of NTD outcomes; or 5) whether MVs contained similar and clinically effective doses of FA. Missing data not accounted for in an ITT analysis; covers a 6 month period of exposure (3 months before to 3 months after pregnancy); No controls for concurrent interventions such as exposure to dietary folate, however, this sample was drawn before dietary supplementation; significant risk of recall bias because women asked to remember for a period ranging from 1968-1980. Only still births, no information on terminations. Cases included live an still-borns controls only - from mulinare

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Bower et al., 1989[143] Bower et al., 1992[144]	Yes	NA	NA	NA	Unclear	High	Cases and controls selected from different populations. Cases could be stillborn infants or elective terminations following antenatal NTD diagnosis, while Control group 1 included liveborn infants and terminated pregnancies with non-NTD malformations and Control group 2 included live born infants only. Possibility of residual confounding because no NTD-specific variables controlled for in analyses. Definition of exposure not defined clearly. Positive response to FA supplement use question could have indicated any frequency of usage. Risk of recall bias because mothers interviewed up to 99 weeks after last menstrual period. Also, minor risk of interviewer bias during 5 interviews because interviewers unintentionally learned case-control status.
Brescianini et al., 2012[145]	Unclear	NA	NA	NA	Unclear	Unclear	Meeting abstract with very little information to base judgment on most domains. Although study does not appear to account for fetal deaths, the resulting selection bias would serve to mute rather than exaggerate the effect of FA on twinning
Carmichael et al., 2010[146]	Yes	NA	NA	NA	Unclear	High	Unclear how missing data was handled; time period extends to 2 months before and 2 months after and with lack of clarity on degree of exposure, difficult to clearly distinguish exposure from non-exposure; authors did not specify definition of exposure clearly (defined as any vs. no supplement), so the degree of adherence is Unclear. The control group only looked at live births and not fetal deaths.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Chandler et al., 2012[147]	Yes	NA	NA	NA	Unclear	Medium	See Yoon et al. (2001) for recruitment info. Cases and controls selected from different populations. Cases could be stillborn infants or therapeutic abortions, while all controls were liveborn infants. Also, definition of exposure not defined clearly. Positive response to FA supplement use question could have indicated any frequency of usage. Possibility of residual confounding because some NTD-specific variables not controlled for, specifically, previous NTD pregnancy or having or having partner(s) with NTDs. In addition, analyses not adjusted for comparisons across different centers.
Charles et al., 2004[148] Charles et al., 2005[149] Taylor et al., 2015[150]	Yes	Yes	Yes	Yes	NA	High	Randomization was inadequate: "tablets were kept in numbered drawers and distributed in sequence." Unclear whether administrators or outcome assessors were blinded because "The patients' notes were marked with a sticker the same colour as the tablets they were receiving." Some proportion of deaths not linked to patient files (occuring before 1980) but followup N not reported, so rate of overall attrition and differential attrition is unclear. Because N at followup is not reported, it does not appear that the analysis used an intention-to-treat analysis for the missing data.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Correa et al., 2012[114]	Yes	NA	NA	NA	No	High	Unclear how missing data was handled but appears to have been excluded in some tables. Definition of exposure does not account for adherence to meds ("any use during the month before conception or during the first 3 months of pregnancy) so exposed vs. non-exposed not clearly demarcated; additionally, the time period of recall is 1 month before conception to 3 months after, so folic acid supplementation after becoming aware of pregnancy would be misclassified as pre-pregnancy exposure; mothers interviewed up to 24 months after birth so risk of recall bias; Authors did not specify definition of exposure clearly, so the degree of adherence is Unclear. Contols were only live borns
Czeizel et al., 2004[151]	Yes	NA	NA	NA	Unclear	High	Does not mention how missing data was handled. Unclear who authors determined who were clearly users of folic acid. Unable to determine response rate due to limited information. Women continued folic acid usage until at least 3rd trimester. There was only one product of folic acid at the time of the study (3mg) and required a prescription. Unclear on baseline differences and if they were controlled for.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Czeizel et al., 2004[74]	Yes	Yes	Yes	Yes	Unclear	Medium	The trial recruited patients to each arm differently. Supplemented women were recruited before pregnancy and asked to take vitamins and were followed up for several months. This recruitment before exposure and continuous measurement would have meant that all prengnancies and terminations would have been counted. Unsupplemented women were identified at 8–12 weeks of pregnancy, by which time, early pregnancy losses would have occured (possibly due to lack of FA). Because one arm differentially identified women, this could have potentially led to a high and differntial risk of selection bias, but the study restricted the analysis for supplemented cases with a pregnancy at 14 weeks. Thus the risk of diffeential selection bias was reduced but the risk of attrtiion bias was increased. A second potential source of bias arises from the residual confounding effects of having a higher proportion in the supplemented group of previous fetal deaths and in fact mortality because of congenital abnormalities.
Czeizel et al., 1992[81]; Czeizel et al., 1993[85]	Yes	Yes	Yes	Yes	NA	Medium	Does not include fetal death in the analysis (but provides data for that calculation; Unclear allocation concealment and blinding processes (participants blinded, Unclear whether administrators or outcome assessors were blinded); does not conduct ITT but dropout extremely low so risk of bias low from dropout. Study did not consider diet and did not mention how missing data was handled.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Czeizel et al., 1996[152]	Yes	NA	NA	NA	No	High	Does not include fetal deaths; study does not control for dietary intake but this study predates food fortification; relevant analysis (supplementation vs. no supplementation in NTD in critical period vs. healthy births) does not control for confounding; does not measure adherence. Unclear on how missing data was handled.
Czeizel et al., 2004[74]	Yes	Yes	Yes	Yes	Unclear	Medium	The trial recruited patients to each arm differently. Supplemented women were recruited before pregnancy and asked to take vitamins and were followed up for several months. This recruitment before exposure and continuous measurement would have meant that all pregnancies and terminations would have been counted. Unsupplemented women were identified at 8-12 weeks of pregnancy, by which time, early pregnancy losses would have occurred (possibly due to lack of FA). Because one arm differentially identified women, this could have potentially led to a high and differential risk of selection bias, but the study restricted the analysis for supplemented cases with a pregnancy at 14 weeks. Thus the risk of differential selection bias was reduced but the risk of attrition bias was increased. A second potential source of bias arises from the residual confounding effects of having a higher proportion in the supplemented group of previous fetal deaths and infant mortality because of congenital abnormalities.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Czeizel et al., 2004[151]	Yes	NA	NA	NA	Unclear	High	Does not include fetal deaths; baseline characteristics are not similar; although study controls for some confounders, relevant analysis (supplementation vs. no supplementation in twins before conception vs. singletons) does not fully measure and control for confounding from use of IVF (focuses on ovarian stimulation by clomiphene); study does not control for dietary intake but this study predates food fortification; does not measure adherence. Does not mention how missing data was handled. Unable to determine response rate due to limited information.
De Marco et al., 2011[153]	Yes	NA	NA	NA	Unclear	High	Well-defined outcomes; exposure is slightly outside our period of interest (i.e., 3 months prior to pregnancy, rather 2 months prior to pregnancy). Possibility of residual confounding because some NTD-specific variables not controlled for, specifically, use of antiepileptic drugs or having or having partner(s) with NTDs. Investigators measured percentages of mothers with previous NTD-affected pregnancies, but relationship to outcomes of interest unlikely (see pg. 1080). In addition, dietary folate intake either not assessed or not taken into account in analyses. Risk of recall bias because mothers completed interviews 18-24 months after childbirth. Unclear how missing data affected findings.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
DeSoto et al., 2012[154]	Yes	Yes	NA	NA	Unclear	High	Definition of FA exposure not defined clearly. Positive response to FA supplement use question could have indicated any frequency of usage. High risk of recall bias because mothers asked about FA use 6-13 years after childbirth. In addition, dietary folate not taken into account. Unclear if important confounders related to ASD included in statistical analyses.
Ericson et al., 2001[155]	Yes	Yes	Unclear	Yes	Unclear	High	Participation rates not reported; unclear whether the two groups are actually comparable-one group included multivitamin use only but whether folic acid was in vitamins and the amount is unclear; also unclear whether those taking folic acid tablets were or were not also taking multivitamins with folic acid.
Gildestad et al., 2013[156]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Not enough information to assess ROB. Only abstract available.
Haberg et al., 1994[157]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Not enough information to assess ROB. Only abstract available.
Hernandez et al., 2001[88]	Yes	NA	NA	NA	Unclear	Medium	Possibility of residual confounding because numerous NTD-specific variables not controlled for, specifically, diabetes, family history of NTDs, prior NTD-affected pregnancy, or having or having partner(s) with NTDs. Dietary folate intake not accounted for in analysis of interest. Authors make point in Discussion that unaccounted effects of folate intake would reduce the magnitude of their findings, which were statistically significant. Outcome assessors blind to study hypothesis, but that does not mean they were blind to womens' case-control status.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Kallen et al., 2004[158]	Yes	Yes	Yes	Yes	Unclear	High	Exposure period starts before pregnancy and extends to first attendance (in 90% of cases before the end of the first trimester and usually around week 10) with lack of clarity on degree of exposure, difficult to clearly distinguish exposure from non-exposure; authors did not specify definition of exposure clearly (defined as any vs. no supplement), so the degree of adherence to MV is Unclear; although study does not appear to account for fetal deaths, the resulting selection bias would serve to mute rather than exaggerate the effect of FA on twinning; study does not control for dietary intake but this study predates food fortification; study does not control for dietary intake but this study predates food fortification; study controls for use of ovarian stimulation drugs, but this control variable is insufficient because fertility treatment includes several other options
Kallen et al., 2007[159]	Yes	Yes	Yes	Yes	Unclear	High	Response rate unclear - percentage of women approached who agreed to participate is Unclear. Also, total number of eligible women is Unclear. Women were recruited at the first antenatal visit, but the total number of women presenting for care during the time period is Unclear. Also, the extent of folic acid not ascertained from participants.
Kondo et al., 2015[160]	Yes	NA	NA	NA	No	High	Selection bias from being limited to live births. Definition of FA exposure not defined clearly. Positive response to FA supplement use question could have indicated any frequency of usage. High risk of recall bias because half of the control and case mothers asked about FA use 6–12 years after childbirth. In addition, dietary folate not taken into account. Controls and cases not matched on year or place of birth, statistically significant differents in knowledge of FA benefits.

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Medvezky et al., 2003[161]	Yes	NA	NA	NA	Unclear	High	Unclear how missing data handled. Exposure not well defined or quantified
Mills et al., 1989[89]	Yes	NA	NA	NA	Unclear	Medium	Eligibility criteria for cases Unclear because they do not clarify whether infants or fetuses were eligible if stillborns or had been aborted. Possibility of residual confounding because numerous NTD-specific variables not controlled for, specifically, diabetes, family history of NTDs, prior NTD-affected pregnancy, having or having partner(s) with NTDs, or treatment with FA antagonists. Unclear how high response rates for control groups were. Unclear how missing data was handled.
Moore et al., 2003[91] Milunsky et al., 1989[90]	Yes	Unclear	Yes		Unclear	Medium	Physicians provided 76.5% of the outcome data, but if physicians did not respond, mothers completed the outcome questionnaires; information provided by mothers may not have been entirely accurate in terms of prenatal test results, presence of birth defects or chromosomal abnormalities, complications of pregnancy or delivery, complications of the newborn, or perinatal maternal illnesses. Treatment fidelity not entirely clear, specifically weekly frequency of folic acid supplementation. Possibility of residual confounding because use of folic acid antagonists not taken into account in analyses. Not enough information provided to calculate differential attrition, but overall attrition rate was very low for full sample and therefore unlikely to bias findings
Mosley et al., 2009[80]	Yes	NA	NA	NA	Yes	Medium	Exposure not well defined or quantified. Response rates didn't approached 80% but relevant, without major apparent selection or diagnostic work-up bias

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Mulinare et al., 1988[162]	Yes	NA	NA	NA	No	High	Missing data not accounted for in an ITT analysis;covers a 6 month period of exposure (3 months before to 3 months after pregnancy); No controls for concurrent interventions such as exposure to dietary folate, however, this sample was drawn before dietary supplementation; significant risk of recall bias because women asked to remember for a period ranging from 1968-1980. Only still births, no information on terminations. Cases included live an still-borns controls only
Ohya et al., 2011[163]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Overall Unclear ROB, not enough information in publication to judge risk of bias
Shaw et al., 2002[164]	Yes	NA	NA	NA	Unclear	High	Unclear how missing data was handle, did not adjust for potential NTD confounders; wide range between those who actually used vitamin (did they use vitamin or mineral supplements during 4 month period but does not say how they divided group out), study does consider cereal usage but not other forms of dietary folate. Potential recall bias - 3.7 to 3.9 years later. Does not mention miscarriages and stillbirths.
Shaw et al., 1995[75]	Yes	NA	NA	NA	Unclear	Medium	3 months before and 3 months after; did not control for all of the confounders we are interested on folate antagonist medications; does not mention miscarriages and stillbirths differences based on ethnicity, age, and education but study control for no mention of how missing data was handled

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Suarez et al., 2000[20]	Yes	NA	NA	NA	Unclear	Medium	1) Response rate less than 80%; 2) some selection bias as controls do not include recruitment at all of the same centers; 3) study collects data on dietary folate intake, but no data shown of association of folic acid with NTDs, adjusted for dietary intake.Strength is adjustment for other confounders. Several issues: (1) very low prevalence of folic acid supplements, limited power (2) food frequency questionnaire doesn't distinguish 3 mos. prior to conception (3) differential recall period produced by not matching case and control infants/fetuses for gestational age (control women recalling exposures further in past than case women); (4) different response rate between case (72%) and control (53%)
Veeranki et al., 2014[165]	Yes	Yes	Yes	Yes	Unclear	High	Exposure to multivitamin supplement defined as filling rather than consuming prenatal vitamins; assumes no misclassification from consumption of over-the-counter supplements; also needed only 1 day of fill in period of exposure to count as exposed; differences between exposed (G1) and non-exposed (G3) in prenatal care, maternal asthma, number of siblings: does not separate out the potential effect of folic acid specifically from other micronutrients that may have an independent effect on respiratory outcomes; does not control for dietary folate exposure; does not control for environmental exposure; excludes stillbirths and miscarriages so risk of selection bias; because of definition of exposure, Unclear whether time period of fill for first trimester covers the first month of pregnancy); loss through poor response rate or missing data NR so cannot judge attrition bias

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Veeranki et al., 2014[166]	Unclear	No	Unclear	Yes	Unclear	High	Exposure to multivitamin supplement defined as filling rather than consuming prenatal vitamins; assumes no misclassification from consumption of over-the-counter supplements; does not separate out the potential effect of folic acid specifically from other micronutrients that may have an independent effect on allergic rhinitis; does not control for dietary folate exposure; does not control for environmental exposure; excludes stillbirths and miscarriages so risk of selection bias; because of definition of exposure, Unclear whether time period of fill for first trimester covers the first month of pregnancy); may not include all cases of allergic rhinits
Veeranki et al., 2015[167]	Yes	No	Yes	Yes	Unclear	High	Exposure to multivitamin supplement defined as filling rather than consuming prenatal vitamins; assumes no misclassification from consumption of over-the-counter supplements; also needed only 1 day of fill in period of exposure to count as exposed; differences between exposed (G1) and nonexposed (G3) in prenatal care, maternal asthma, number of siblings: does not separate out the potential effect of folic acid specifically from other micronutrients that may have an independent effect on respiratory outcomes; does not control for dietary folate exposure; does not control for environmental exposure; excludes stillbirths and miscarriages and preterm, so risk of selection bias; because of definition of exposure, Unclear whether time period of fill for first trimester covers the first month of pregnancy; loss through poor response rate or missing data NR so cannot judge attrition bias; may not include all cases of asthma

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Vollset et al., 2005[76]	Yes	Yes	Yes	Yes	Unclear	Medium	Risk of recall bias in original data assumed to be high - based on estimates of underrreporting of folate use, they estimated that 45% of women who took folate before conception were registered as nonusers and adjusted potential misclassification as a result; however, periconceptional use not defined, as a result, cannot tell if exposed vs. non-exposed is clearly defined; looks at pregnancies, but Unclear how stillbirths and terminations were handled; no adjustment for dietary folate; because of lack of definition of exposure, Unclear whether time period of fill for first trimester covers the first month of pregnancy); loss through poor response rate or missing data NR so cannot judge attrition bias

Table D7. Risk of bias assessments for all included randomized controlled trials, case control studies, and cohort studies (Part 5) (continued)

First Author, Year	Were outcomes pre-specified/ defined and adequately described?	Were outcome measures valid and reliable?	Were all important outcomes considered?	Was the duration of follow-up adequate to assess the outcome?	Was an appropriate method used to handle missing data?	Risk of Bias Rating	Comments
Werler et al., 1993[92]	Yes	NA	NA	NA	No	Medium	Cases and controls identified by "systematic contact" at tertiary and birth hospitals, details NR, as a result, unable to determine whether cases and controls came from similar populations and had a similar chance of selection; looked at the effect of dietary intake of folate, but only for those with no use of supplements, so does not fully control for concurrent interventions;

G1 = group 1; G3 = group 3; NA = not applicable; NR = not reported; NTD = neutral tube defect

Low: Meets all criteria: Comparable groups are assembled initially and maintained throughout the study (follow-up at least 80%; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, for RCTs, intention to treat analysis is used.

Medium: Studies will be graded "medium" if any or all of the following problems occur, without the fatal flaws noted in the "high" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are accounted for. Intention to treat analysis is done for RCTs.

High: Studies will be graded "high" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied at all equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.

Appendix E. Inclusion/Exclusion Status of Studies Included in 2009 Report

Table E-1: Overview of 2009 included studies and inclusion/exclusion status in current report

First Author, Year	Status in Current Report	Reasons for Exclusion
Czeizel et al., 2004[74]	Included	
Goh et al., 2006[77]	Excluded	Excluded due to high risk of bias
Shaw et al., 1995[75]	Included	
Thompson et al., 2003[78]	Excluded	Excluded for wrong intervention. Unable to separate out the effects of supplementation from diet.
Vollset et al., 2005[76]	Included	

Table E-2. Overview of studies excluded from the 2009 report due to quality and inclusion/exclusion status in current report

First Author, Year	Reasons for 2009 Exclusion	Status in Current Report	Reasons for Exclusion
Czeizel et al., 1996[152]	Retrospective exposure assessment poses potential recall bias. Differential measurement of exposure causes potential measurement bias. Lower response rate in controls No adjustment for smoking	Excluded	Excluded for high risk of bias
Locksmith et al., 1998[168]	Study type not included in review (not a systematic review)	Excluded	Excluded for wrong design
Kallen et al., 2002[169]	Used involuntary childlessness as proxy for infertility Exposure assessed by questionnaire at gestational week 10–12: drugs taken "since she became pregnant" No information about dose, timing	Excluded	Excluded for wrong comparator
Lumley et al., 2001[170]	Studies included were not recent (many published prior to 1995 and included in USPSTF previous evidence report).	Excluded	Excluded for wrong population
Medveczky et al., 2004[161]	No information on overall effect of folic acid on NTDs	Excluded	Excluded for high risk of bias
Moore et al., 2003[91]	This was a study of dose-response re-examining data from study reviewed in 1996 USPSTF report; no new information about overall benefits of folic acid supplementation	Included	Even though the previous report listed it as an exclude "after abstraction and quality rating", the notes in the abstraction form indicate "This was a study of dose-response re-examining data from study reviewed in 1996 USPSTF report; no new information about overall benefits of folic acid supplementation
Shaw et al., 2002[164]	No information on overall effect of folic acid on NTDs	Excluded	Excluded for high risk of bias
Shaw et al., 1998[171]	No information on overall effect of folic acid on NTDs	Excluded	Excluded for wrong outcome
Shaw et al., 2001[172]	No information on overall effect of folic acid on NTDs	Excluded	Excluded during title/abstract review
Shaw 1996[173]	No information on overall effect of folic acid on NTDs	Excluded	Excluded during title/abstract review
Suarez et al., 2000[20]	Study performed in high-risk population	Included	Even though the previous report listed it as an exclude "after abstraction and quality rating", the notes in the abstraction form indicate that was excluded for "high-risk populations" - that is, the population of Mexican-Americans have a higher risk of NTDs

Table E-2. Overview of studies excluded from the 2009 report due to quality and inclusion/exclusion status in current report (continued)

First Author, Year	Reasons for 2009 Exclusion	Status in Current Report	Reasons for Exclusion
Ericson et al., 2001[155]	Potential confounding by patients undergoing IVF or ovulation stimulation; subgroup analysis on women without "period of involuntary childlessness", but authors reported known underreporting of infertility history (40% of women who underwent IVF or ovulation stimulation did not report involuntary childlessness.) Measurement validity issues: exposure measured at 10 weeks; reported folic acid use was 0.6% in this study based on Birth Registry, as compared to 8% in concurrent study. No information on doses or timing of initiation of folic acid Potential differential recall based on knowledge of twin gestation by 8–10 weeks	Excluded	Excluded for high risk of bias
Czeizel et al., 2004[151]	No adjustment for possible confounders: IVF, ovulation induction, smoking No information on doses or timing of initiation of folic acid Potential differential recall based on knowledge of twin gestation early in pregnancy or twin delivery	Excluded	Excluded for high risk of bias
Kallen et al., 2004[158]	Incomplete information on doses (women likely took either 400 micrograms or 5 mg) or whether prenatal vitamins with folic acid were included in analysis No information on timing of initiation or duration of exposure Initial comparability of groups unknown Potential differential recall based on knowledge of twin gestation by 8–10 weeks Residual confounding possible if incomplete reporting of fertility treatments. Unclear how many women were included in the final analysis.	Excluded	Excluded for high risk of bias

Appendix F. Overview of Study Characteristics

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Agopian et al., 2012[9] National Birth Defects Prevention Study Case-control United States Centers for Disease Control and Prevention and Texas Department of State Health Services Medium	Included: National Birth Defects Prevention Study (NBDPS), data collected from population-based surveillance systems located in 10 states: Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Cases included live births, fetal deaths, and elective pregnancy terminations. Live born controls without major birth defects were ascertained through birth certificate data or hospital birth logs. Controls were selected at random among infants delivered in the study regions. Excluded: Cases with additional major birth defects that were unlikely to be secondary to the NTD. Excluded potential cases with single-gene disorders or chromosome abnormalities	G1: Spina bifida or anencephaly live births, fetal deaths, and elective pregnancy terminations (n = 1239) G2: Live born controls without major birth defects (n = 8494)	Folic acid supplementation before pregnancy through 1st month of pregnancy Population-based surveillance systems in 10 states. Data collected from medical records, birth certificate data, or hospital birth logs.	NR	42%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Ahrens et al., 2011[11] SSlone Birth Defects Study Case-control United States Centers for Disease Control and Prevention Medium	Included: Slone Birth Defects Study, infants with birth defects were identified from discharge records of participating hospitals serving the areas surrounding Boston, MA; Philadelphia, PA; San Diego, CA; and Toronto, Canada; in addition, cases have been identified through birth defect registries in Massachusetts and parts of New York State. Nonmalformed controls have been randomly selected each month from study hospitals' discharge lists or from statewide birth records. Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation were eligible as cases for our study. Only live-born nonmalformed infants were eligible as controls.	G1: Malformed live-born infants, therapeutic abortions after 12 weeks' gestation, and fetal deaths after 20 weeks' gestation (n= 205) G2: Live-born nonmalformed infants (n = 6357)	Folic acid supplementation 2 months before the last menstrual period and 1 month after last menstrual period. Cases identified from discharge records of participating hospitals serving the areas surrounding Boston, MA; Philadelphia, PA; San Diego, CA; and Toronto, Canada and through birth defect registries in Massachusetts and New York State. Nonmalformed controls selected each month from study hospitals' discharge lists or from statewide birth records.	Median age at conception G1: 28 G2: 30	29%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Czeizel et al., 1992[81] Czeizel et al., 1993[82] Czeizel et al., 1994[83] Czeizel et al., 1994[84] Czeizel et al., 1993[85] Czeizel et al., 1996[87] Czeizel et al., 1998[86] Hungarian RCT RCT Hungary NR Medium	Included: Women planning a pregnancy, did not have delayed conception or infertility, not currently pregnant. During the first four years of trial women had to be less than 35 years old and no previous wanted pregnancy.[83] Excluded: Patients with genetically determined syndromes, including those involving NTDs (e.g., Meckel's syndrome or Patau's syndrome).[81]	G1: Vitamin supplement (0.8 folic acid and 12 vitamins, 4 minerals, 3 trace elements)[86] (n= 2793) G2: Trace-element supplement (copper, manganese, zinc, low dose of vitamin C)[87] (n = 2660)	28 days before conception and at least until the date of the second missed menstrual period[84] Hungarian Preconceptional Service (HPS) began 3 months before a pregnancy tis planned and continues for the first 3 months after conception. HPS provided information and counseling, examinations, and interventions during all trimesters by qualified nurses.	27	NR

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Czeizel et al., 2004[74] Hungarian Cohort-Controlled Trial Cohort-controlled trial Hungary NR Medium	Included: Supplemented cohort was recruited from the Hungarian Periconceptional Service between May 1, 1993 and April 30, 1996. Routine care subjects for an unsupplemented cohort were recruited during their first visit at an antenatal care clinic between the 8th week and 12th week of gestation. Excluded: Supplemented group: did not conceive within one year. Unsupplemented group: multivitamin and/or folic acid use during the periconceptional period and before first visit.	G1: Women supplemented with multivitamin (n = 3056) G2: Nonsupplemented women (n = 3056)	Before conception and at least until first missed menstrual period. Supplemented cohort was recruited from the Hungarian Periconceptional Service (HPS). HPS provides information and counseling, examinations, and interventions during all trimesters by qualified nurses. Unsupplemented cohort was recruited during their first visit at an antenatal care clinic.	27	NR

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Hernandez-Diaz et al., 2001[88] SSlone Epidemiology Unit Birth Defects Study Case-control United States Pharmacoepidemiology Teaching and Research Fund of the Harvard School of Public Health: the National Center for Environmental Health, Centers for Disease Control and Prevention; the Massachusetts Department of Public Health: the National Institute of Child Health and Human Development and the National Heart, Lung, and Blood Institute Medium	Inclusion: Slone Epidemiology Unit Birth Defects Study. Cases, infants and fetuses with anencephaly, spina bifida, encephalocele, or other NTDs. Controls, infants with malformations other than NTDs. Excluded: Infants with chromosomal or Mendelian-inherited anomalies or with amniotic bands, caudal regression, or twin disruption. Subjects with oral clefts, urinary tract defects, limb reduction, heart defects, and conditions related to NTD (hydrocephalus, microcephalus, and other anomalies of the brain, spinal cord, or nervous system).	G1: Cases with NTDs (spina bifida, anencephaly, and encephalocele, or other NTDS) (n=1242) G2: Infants with malformations not related to vitamin supplementation (n=6660)	Any time during the 2 months after the last menstrual period. Participants of the Slone Epidemiology Unit Birth Defects Study. Study interviewed mothers of malformed children born in the greater metropolitan areas of Boston, Massachusetts, Philadelphia, Pennsylvania, Toronto, Canada, and, between 1983 and 1985, part of the state of Iowa. Subjects identified through review of admissions and discharges at major referral hospitals and clinics and through regular contact with newborn nurseries in community hospitals A random sample of nonmalformed infants was identified at the birth hospitals as potential controls (only after 1993).	Overall Percentages < 24:28.11% 25-29:36.71% 30-34:25.87% >35: 9.3%	2%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Mills et al., 1989[89] National Institute of Child Health and Human Development Neural Tube Defects Study Case-control United States Funding NR, conducted by NIH. Medium	Inclusion: National Institute of Child Health and Human Development Neural Tube Defects Study based in CA and IL. Cases, mothers of an infant or fetus with an NTD diagnosis prenatally or postnatally between June 15, 1985 and April 30, 1987 in IL or between August 1, 1985 and April 30, 1987 in CA. NTDs included anencephaly, meningocele, myelomeningocele, encephalocele, rachischisis, iniencephaly, and lipomeningocele. Two controls, one mothers of a normal infant or fetus and one mothers of an abnormal or still-born infant or fetus. Exclusion: Cases excluded insolated hydrocephalus, hydranencephaly, dermal sinus, and spina bifida occulta. Abnormal control group excluded mothers of infants with malformations related to vitamin use. Mothers with a history of neural-tube defects in a first-degree relative was excluded from both control groups.	G1: Cases, mothers of an infant or fetus with a neutral-tube defect (n= 571) G2: Controls, mothers of normal infants (n=573) G3: Controls, mothers of an abnormal or still-born infant or fetus (n=546)	Vitamin use 30 days before the first day of the last menstrual period and ending approximately 45 days thereafter. Study based in CA and IL. Cases included mothers of an infant or fetus with an NTD diagnosis prenatally or postnatally between June 15, 1985 and April 30, 1987 in IL or between August 1, 1985 and April 30, 1987 in CA.	< 21: 11.60% 21-25: 25.92% 26-30: 34.14% 31-35:20.18% 36-40:7.04% 41-45: 1.01% Unknown: 0.12%	39%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Milunsky et al., 1989[90] Moore et al., 2003[91] Cohort United States Study 1: National Institute of Neurological Disorders and Stroke Study 2: March of Dimes Birth Defects Foundation; National Institute of Neurological Disorders and Stroke Medium	Inclusion: Women were identified and recruited when they had a maternal serum a-fetoprotein (MSAFP) screen or an amniocentesis. They were receiving prenatal care and routine MSAFP screening in the practices of over 100 participating obstetricians. MSAFP and amniotic fluid samples were analyzed at the Center for Human Genetics of Boston University School of Medicine. Remaining amniocenteses were performed and analyzed at other genetic centers throughout the country and the results were made available to the researchers. Exclusion: Interviews of mothers pregnant a 2nd or 3rd time during study were excluded.	G1: Use of multivitamins containing folic acid G2: No use of multivitamins containing folic acid (or use less than 1 a week) Total: (n=22715, multivitamin use information available)	3 months prior to pregnancy through 1st 3 months of pregnancy Women were identified and recruited when they had a maternal serum a-fetoprotein (MSAFP) screen or an amniocentesis at 16 weeks of pregnancy between October 1984 and June 1987. Women were receiving prenatal care and routine MSAFP screening in the practices of over 100 participating obstetricians.	Study 1 < 20: 2% 20-29: 44% 30-39: 52% 40 years or above: 2% Study 2 < 30: 2% 30-39: 44% 40 years or above: 2%	Study 1: 4% Study 2: NR

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Moseley et al., 2008[80] National Birth Defects Prevention Study Case-control United States Centers for Disease Control and Prevention Medium	Inclusion: National Birth Defects Prevention Study, began in 1997 and includes participants from 10 population-based birth defects surveillance systems (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, or Utah). Cases, pregnancy affected by anencephaly or spina bifida that did not result from a single gene or chromosomal abnormality. Controls, random sample of women from each center site who delivered a liveborn infant without a structural birth defect. Included pregnancies were conceived on or after July 1, 1998. Exclusion: Women with type 1 or type 2 diabetes or use of periconceptional use of any folate antagonist medication. Pregnancies resulting in multiple births. Women with incomplete food frequency questionnaires or supplement use information.	G1: Women with a pregnancy affected by spina bifida or anencephaly that did not result from a single gene or chromosomal abnormality G2: Women who delivered a live-born infant without a structural birth defect	Folic acid supplementation 3 months before pregnancy through 1st month of pregnancy Population-based surveillance systems in 10 states. Data collected from medical records, birth certificate data, or hospital birth logs.	Median age at conception G1: 26 G2: 27	42%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Shaw et al., 1995[75] California Birth Defects Monitoring Program Case-control United States NR Medium	Inclusion: California Birth Defects Monitoring Program (CBDMP): birth years between June 1, 1989 and May 31, 1991. Cases: women who had liveborn and stillborn infants with NTDs; place of delivery in California county other than Los Angeles, Ventura, or Riverside; mother was a resident of California; and those who had NTD-affected pregnancies that were terminated. Controls: singletons born alive in the specified month and year in that hospital; mother was a resident of California; and no reportable birth defect. Exclusion: Women who spoke only languages other than English or Spanish. Previous NTD affected pregnancies.	G1: Singleton liveborn infants and electively terminated fetuses with an NTD (anencephaly, spina bifida cystica, craniorrhachischisis, and iniencephaly) (n = 538) G2: Singleton live births without a reportable birth defect (n = 539)	3 months before pregnancy and/or first 3 months after conception California Birth Defects Monitoring Program (CBDMP), birth years between June 1, 1989 and May 31, 1991. Cases were women who had liveborn and stillborn infants with NTDs, and those who had NTD-affected pregnancies that were terminated after prenatal diagnosis (February 1, 1989-January 31, 1991). Controls were an equal number of singleton live births randomly selected in proportion to hospital's contributions to total population of infants born alive in California.	Overall <20: 10.86% 20-24: 27.21% 25-29: 29.80% 30-34: 22.47% 35 and over: 9.66 %	54%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Suarez et al., 2000[20] Texas Department of Health's Neural Tube Defect Project United States Centers for Disease Control and Prevention Medium	Inclusion: Texas Department of Health's Neural Tube Defect Project, projects occurs in 14 Texas counties along the US-Mexico border. Cases, infants or fetuses with anencephaly (including craniorachischisis and iniencephaly), spina bifida, or encephalocele identified at birth or prenatally between January 1995 and February 1999. Cases included diagnoses made among liveborns, stillborns, and fetuses at all gestational ages, and included abortions, whether induced or spontaneous. Control, women from study area who had normal births during the same time period. Exclusion: Controls were ineligible if they were not a resident of the area or if they had an infant with an apparent or prenatally diagnosed congenital abnormality	G1: Infants or fetuses who had anencephaly (including craniorachischisis and iniencephaly), spina bifida, or encephalocele identified at birth or prenatally (n=148) G2: Normal live births (n= 158)	3 months before conception to 3 months after conception Texas Department of Health's Neural Tube Defect Project, occurrence of NTDs in 14 Texas counties along the US-Mexico border identified at birth or prenatally between January 1995 and February 1999. Surveillance included hospitals, birthing centers, genetics clinics, ultrasound centers, licensed abortion centers, and approximately midwives in the region.	< 20: 25.50% 20-24: 32.68% 25-29: 24.84% >30-39:16.99%	100%

Table F-1. Characteristics of Included Randomized controlled trials, case-control, and cohort studies (continued)

First Author Study Name Design Country Funding Risk of Bias	Inclusion Exclusion Criteria	Groups	Timing Setting	Mean Age	% Nonwhite
Vollset et al., 2005[76] Medical Birth Registry of Norway Case-control Norway NR Medium	Inclusion: Medical Birth Registry of Norway, women who gave birth from December 1998 through the end of 2001. Information on IVF pregnancies obtained by contacting fertility clinics in Denmark and Sweden. Exclusion: NR	G1: Preconceptional use of folate (n = 11,077) G2: No preconceptional use of folate (n = 164,965)	Preconception Medical Birth Registry of Norway, women who gave birth from December 1998 through the end of 2001. Information on IVF pregnancies obtained by contacting fertility clinics in Denmark and Sweden.	NR	NR
Werler et al., 1993[92] Case-control United States and Canada Maternal and Child Health Resources Development grant; Marion Merrell Dow, Inc; US Food and Drug Administration Cooperative Agreement; Hoffmann-LaRoche, Inc Medium	Inclusion: Study subjects (liveborn and stillborn infants and therapeutic abortuses) recruited from tertiary and birth hospitals in greater metropolitan Boston, MA, Philadelphia, PA, and Toronto, Ontario. Primary physicians of potential subjects were asked for permission to contact mothers. Cases: subjects with anencephaly, spina bifida, or encephalocele. Controls: subjects with other major malformations. Exclusion: Subjects with chromosomal anomalies or mendelian-inherited disorders; recurrent NTD cases; oral clefts.	G1: Liveborn, stillborn infants, and therapeutic abortions with anencephaly, spina bifida, or encephalocele (n= 436) G2: Liveborn, stillborn infants, and therapeutic abortions with other major malformations (n=2615)	Periconceptional period (interval from 28 days before the last menstrual period (LMP) through the 28 days after the LMP (the first lunar month). Study subjects recruited from tertiary and birth hospitals in greater metropolitan Boston, MA, Philadelphia, PA, and Toronto, Ontario. Primary physicians of potential subjects were asked for permission to contact mothers.	NR	NR

G1 = group 1; G2 = group 2; G3 = group 3; N = sample; NR = not reported; NTD = neural tube defect

Table F-2. Characteristics of Included systematic reviews and meta-analyses

First Author Study Design Search Dates Country Funding	Eligibility Criteria	Studies Included in Review	Included Study Designs	Intervention Dose Time Period	Overall Sample Size	Countries Included
Crider et al., 2013[94] SR/Meta-analysis Inception of database to March 2012 United States CDC	1) Randomized controlled trial, cohort, case-control, or cross-sectional study; 2) report the exposure of natural food folate intake, folic acid intake from fortified foods, total folate intake from foods (eg, dietary folate equivalents), folic acid intake from supplements, or maternal or cord blood serum, plasma, or red blood cell folate concentrations; 3) have an exposure timing during the periconceptional period or during pregnancy; 4) provide results on at least one allergic or respiratory outcome; and 5) include an evaluation of the direct association between folic acid exposure and one of the outcomes of interest	5 in meta-analysis Ha°berg et al., 2009[95] Kiefte-de Jong et al., 2012[96] Magdelijns et al., 2011[97] Martinussen et al., 2012[98] Whitrow et al., 2009[99]	10 cohort studies, 3 nested case-control studies, 1 case-control, 2 cohort, 2 case-control	Folic acid supplementation 400-500 µg/d Prepregnancy and first trimester	45642	Netherlands, Norway, Australia, United States
Yang et al., 2015[101] Meta-analysis Earliest available date to May 2013 China NR	Exposure was maternal folic acid supplementation during pregnancy; outcome was infant asthma; analytical study (case–control studies or cohort studies); available multivariate-adjusted relative risks (RRs), hazard ratios (HRs) or odds ratios (ORs) with 95% confidence intervals (CIs); unrelated case and control groups or exposed and unexposed groups in a cohort study and all subjects from the same temporally and geographically defined underlying population.	Bekkers et al., 2012[93] Granell et al., 2008[100] Magedlijns et al., 2011[97] Martinussen et al., 2012[98] Whitrow et al., 2009[99]	5 cohort studies	Folic acid supplementation Range NR Prepregnancy	14438	Australia, The Netherlands, United Kingdom

G1 = group 1; G2 = group 2; N = sample; NR = not reported; NTD = neural tube defect.

Appendix G. Ongoing Trials

Principal investigators	Location	Population	Approximate size	Investigations	Outcomes	Status as of 2015
Renata Bortolus, MD	Italy	Females 18-44 who intend to become pregnant	5000	4mg/day vs. 0.4 mg/day	Number of congenital malformations Rate of selected congenital malformations Miscarriages and recurrent abortions Pre-eclampsia Abruption placenta Intrauterine growth restriction Pre-term delivery Multiple births	Recruiting; Estimated Study completion: September 2016
Fenneke Blom, PhD	The Netherlands	Females 18-45 who want to become pregnant within 12 months	5000	4mg/day vs. 0.4 mg/day	Folic acid related congenital anomalies Preterm birth Birth weight Preeclampsia Compliance with intervention	Recruiting; Estimated Study completion: December 2016

vs. = versus.