National Institute for Health and Care Excellence

Final

Maternal and child nutrition

[A] Evidence reviews for high-dose folic acid supplementation before and during the first 12 weeks of pregnancy

NICE guideline NG247

Evidence reviews underpinning recommendations 1.1.5, 1.1.7 and the recommendation for research on high-dose folic acid supplementation in the NICE guideline

January 2025

Final

These evidence reviews were developed by NICE

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-6761-2

Contents

High-dose folic acid supplementation before and during the first 12 weeks of pregnancy

Review question

Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Introduction

There is uncertainty as to which high risk groups may benefit from a higher dose (5 mg) of folic acid to help reduce the risk of neural tube defects (NTDs) and this uncertainty has led to variations in international guidance. The WHO and NICE guidance both recommend a higher dose folic acid supplement and increased food intake of folate for those with previous pregnancy affected by NTDs, who have diabetes, or taking anticonvulsant treatment. The aim of this review is to determine which groups should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy.

Summary of the protocol

See Table 1 for a summary of the Population, Intervention, Comparison and Outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women in the preconception stage trying to become pregnant or women during the first 12 weeks of a single or multiple pregnancy
Intervention	High-dose folic acid supplementation (≥5 mg daily) (Alone or in combination with other vitamins and minerals)
Comparison	• Low-dose folic acid supplementation (<1 mg daily) • Medium-dose folic acid supplementation (≥1 to <5 mg daily) • Placebo • No intervention (Alone or in combination with other vitamins and minerals)

Outcome	**Critical:**
	• neural tube defects (NTDs) in the baby
	• birthweight
	• hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension)
	Important:
	• RBC (or serum if RBC is not reported) folate concentrations in the mother
	• neurodevelopmental outcomes (dichotomous outcome, not continuous outcomes such as mean change in score):
	  ○ severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of MDI or PDI)
	  ○ moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84).
	• congenital heart defects
	• midline facial defects such as cleft lip or cleft palate

MDI: mental development index; mg: milligrams; PDI: psychomotor developmental index; RBC: red blood cell; SD: standard deviation

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document (supplementary document 1).

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Effectiveness evidence

Included studies

No evidence was found on high dose folic acid supplementation (≥5 mg/day), the dose currently recommended in the UK for pregnant women at high risk of NTDs. The committee agreed to make a deviation to the protocol and relax the inclusion criteria to include folic acid supplementation of 4 mg/day, in the absence of evidence on dose of ≥5 mg/day, but downgraded the evidence for indirectness.

Three randomised controlled trials were included in this review (Laurence 1981, MRC 1991, Wen 2018).

The included studies are summarised in Table 2.

Two studies reported on women with a history of births with NTDs (Laurence 1981, MRC 1991), and 1 study reported on women at high risk of pre-eclampsia (Wen 2018).

Two studies compared 4 mg folic acid per day to placebo (Laurence 1981, Wen 2018). One study compared 4 mg folic acid per day to placebo and also had a third arm comparing 4 mg folic acid with multivitamins per day to placebo (MRC 1991). In Wen 2018, participants in both arms included women taking daily prenatal vitamins or low dose folic acid supplements (up to 1.1 mg of folic acid) throughout the study period.

One study was conducted in the United Kingdom (Laurence 1981), 1 study was conducted in Australia, Canada, France, Hungary, Israel, Russia and UK (MRC 1991) and 1 study was conducted in Argentina, Australia, Canada, Jamaica and UK (Wen 2018).

There was no evidence available for the following outcomes: birthweight, neurodevelopmental outcomes, congenital heart defects and midline facial defects such as cleft lip or cleft palate outcomes.

As per protocol the evidence was stratified according to women with a previous history of a pregnancy affected by NTDs. Pre-eclampsia was not a stratum in the protocol, however as the risk of neural tube defects in this population is different to those with previous history of NTDs, the committee agreed that women with high risk of pre-eclampsia should be analysed separately. There was not sufficient evidence to stratify evidence based on parity, women taking antiseizure medications, women taking antifolate medications, women with diabetes, and women who started folic acid pre-conception.

As per protocol, subgroup analyses for the following groups was agreed to be conducted if there was heterogeneity: deprived socioeconomic group, age <40 versus ≥40, women and parents with disabilities, including learning disabilities and other physical and mental health conditions, women going through assisted conception, religion, cultural considerations and

ethnicity, and women who smoke versus not. There was no heterogeneity identified in the evidence, hence subgroup analysis was not conducted.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review are listed, and reasons for their exclusion are provided in appendix J.

Summary of included studies

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention	Comparison	Outcomes	Comments
Laurence 1981 RCT UK	N=111 women with a history of births with NTDs Participant characteristics: NR	4mg folic acid Taken as a 2mg tablet, twice a day from the time contraception stopped until birth	Placebo	• Neural tube defects • Red blood cell folate concentration	Follow-up: at birth Strata: history of births with NTDs
MRC 1991 RCT Australia, Canada, France, Hungary, Israel, Russia, UK	N=893 women with a history of births with NTDs Maternal age, mean (SD: NR): Intervention Group A: 27 Group B: 27.4 Control: 26.8 Maternal BMI: NR Livebirths in previous pregnancies, mean: Group A (4mg folic acid): 0.88 Group B (4mg folic acid + multivitamin): 0.94 Group C (placebo): 0.91	Group A: 4mg folic acid Group B: 4mg folic acid + multivitamin Taken as 1 tablet, daily, from randomisation until 12 weeks gestational age	Group C: Placebo Contains dried ferrous sulphate (120mg) and di-calcium phosphate (240mg)	• Neural tube defects	Multivitamin composition: vitamin A 4000 IU, D 400 IU, Bl 1-5mg, B2 1.5 mg, B6 10mg, C 40mg, and nicotinamide 15mg Follow-up: at 12 weeks of pregnancy Strata: history of births with NTDs

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean number of previous NTD pregnancies: Group A (4mg folic acid): 1.03 Group B (4mg folic acid + multivitamin): 1.04 Group C (placebo): 1.01				
Wen 2018 RCT Argentina, Australia, Canada, Jamaica, UK	N=2301 women at high risk of pre-eclampsia Maternal age, mean(SD): Intervention: 31(5.4) Placebo: 31(5.4) Pregnancy BMI, mean (SD) Intervention: 34 (8.6) Control: 34 (13) Parity, n (%): Intervention: 0 - 413 (33.7) 1 - 498 (40.6) ≥2 - 316 (25.7) Control: 0 - 420 (34.0) 1 - 499 (40.4) ≥2 - 317 (25.6) History of pre-eclampsia: Intervention: 308 (25.1) Control: 303 (24.5)	4mg folic acid Taken as a 1mg tablet, 4 times a day from 8 to 16 weeks gestational age until birth	Placebo	• Pre-eclampsia	Participants in both arms were allowed to take daily prenatal vitamins or low dose folic acid supplements (up to 1.1 mg of folic acid). Follow-up: at 42 days postpartum Strata: high risk of preeclampsia

BMI: body mass index; IU: international units; mg: milligrams; µg: micrograms; N/A: not applicable; NR: not reported; NTDs: neural tube defects; RCT: randomised controlled trial; SD: standard deviation

See the full evidence tables in appendix D and the forest plots in appendix E.

Summary of the evidence

Folic acid supplementation 4 mg/day versus placebo in women with a history of births with neural tube defects (NTDs)

Two studies were included under this comparison.

Evidence for 4 mg folic acid per day versus placebo for women with a history of births with NTDs showed that there was an important benefit for 4 mg folic acid per day compared to the placebo for the outcomes of NTDs (at 12 weeks of pregnancy and birth follow-up) and red blood cell folate concentration (at birth follow-up) favouring folic acid supplementation over placebo.

The evidence was of low quality.

Folic acid supplementation 4 mg/day + multivitamin versus placebo for women with a history of births with neural tube defects (NTDs)

One study was included under this comparison.

Evidence for 4 mg folic acid per day plus multivitamins versus placebo for women with a history of births with NTDs showed that there was an important benefit for daily 4 mg folic acid plus multivitamins intake compared to the placebo for the outcome of NTDs at 12 weeks of pregnancy follow-up.

The evidence was of very low quality.

Folic acid supplementation 4 mg/day versus placebo in women at high risk of preeclampsia

One study was included under this comparison.

Evidence for 4 mg folic acid per day versus placebo for women at high risk of preeclampsia showed that there was no important difference between daily 4 mg folic acid intake compared to placebo for the outcome of severe pre-eclampsia at 42 days post-partum follow-up.

The evidence was very low quality.

See appendix F for full GRADE tables.

Economic evidence

Included studies

No economic studies were identified which were applicable to this review question. See the literature search strategy in appendix B and economic study selection flow chart in appendix G.

Excluded studies

No economic studies were reviewed at full text and excluded from this review.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Unit costs

Table 3: Unit costs of folic acid

Resource	Unit costs	Source
Folic acid 5 mg tablets	28 for £0.68	NHS Business Services Authority, NHS Prescription Services. NHS England and Wales. Electronic Drug Tariff. Issue: May 2024. Compiled on the behalf of the Department of Health and Social Care. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff
Folic acid 400 microgram tablets	90 for £3.27	NHS Business Services Authority, NHS Prescription Services. NHS England and Wales. Electronic Drug Tariff. Issue: May 2024. Compiled on the behalf of the Department of Health and Social Care. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Neural tube defects in the baby, birthweight, and hypertensive disorders of pregnancy were prioritised as critical outcomes by the committee. These outcomes were identified as critical because high dose maternal folic acid supplements can reduce the risk of NTDs in the baby and observational studies have suggested a relationship between low maternal folic acid status in the mother with low birthweight and maternal hypertensive disease in pregnancy. The committee agreed that red blood cell folate concentrations in the mother should be an important outcome as it is a critical biomarker for folate status. Congenital heart defects, and midline facial defects were also deemed important outcomes because folic acid protects babies against some birth defects other than NTDs including heart and midline facial defects. Relationships have also been shown between low maternal folate status and neurodevelopmental disorders other than NTDs.

No evidence was identified for relationships between high dose folic acid supplementation and congenital heart defects with midline facial defects, birthweight, neurodevelopmental outcomes other than NTDs.

The quality of the evidence

The quality of the evidence was assessed using GRADE methodology. The quality of the evidence ranged from very low to low quality. The main reasons for downgrading were risk of bias (for example, there were some concerns with bias in selection of the reported result, bias due to missing outcome data, and bias in the measurement of the outcome), imprecision due to small number of events rate and indirectness due to no intervention available of high dose folic acid supplements (≥5 mg) and due to the population including people with body mass index ≥35kg/m^2. Risk of bias was most commonly due to deviations from the intended interventions and missing outcome data.

Studies were assessed for quality using the Cochrane Risk of Bias tool version 2. One study (Wen 2018) included participants and settings that were not directly relevant to the study protocol (that is, women with a BMI ≥35kg/m^2 and trial centres in low and middle income countries (LMICs)). Overall, the population from LMICs was very small and not considered to affect the quality of the evidence, however the evidence was downgraded for indirectness as

>33% of the population had a BMI ≥35kg/m^2. All 3 included studies compared 4 mg/day folic acid supplement with placebo. These studies were downgraded for indirectness as the dose of folic acid did not meet the intervention high dose folic acid supplement threshold in the protocol.

Benefits and harms

Overall, the committee agreed that the evidence base is sparse in this topic area, with no studies identified on high dose folic acid (≥5 mg per day). The committee discussed that 4 mg of folic acid was close to 5 mg and clinically a high dose compared to the standard 400 micrograms.

The committee discussed that current recommendation advising those at higher risk of NTDs to take 5 mg folic acid per day are based on clinical consensus rather than clinical evidence. The committee were aware of information about how and when to take folic acid on the NHS website, which recommends 5 mg folic acid per day for people with folate deficiency anaemia, and discussed that this dose had probably been extended to include pregnant people with a higher risk of NTDs given the availability of this dose in pharmacies. However, this is not only the case in the UK as 5mg dose is commonly recommended in other countries as well to pregnant populations at higher risk of NTDs.

Low quality evidence showed that 4 mg folic acid per day in women with a history of births with NTDs had an important benefit on reducing neural tube defects in the baby and increasing red blood cell folate concentration in the pregnant woman. The committee agreed that ideally they would recommend 4 mg of folic acid for those at higher risk of NTDs because that is based on the available evidence. However, in the UK, the only folic acid formulations available are 400 micrograms and 5 mg and it would be impractical to suggest that people should take 10 of the 400-microgram tablets daily. Folic acid is not a narrow therapeutic index drug, meaning that there is likely no big difference between the 4 mg and 5 mg dose. Furthermore, folic acid is generally well tolerated even in high doses. While evidence on folic acid toxicity among different populations was not reviewed by the committee, it is known that there is no evidence to suggest harm from 5 mg folic acid per day in different populations, although the evidence base is limited. Concerns have been raised about the potential exacerbation of neuropathy in individuals with vitamin B12 deficiency when treated with high dose folic acid, instead of vitamin B12. However, this analysis appears to have been incorrect (Wald 2018). Regardless, this has little relevance for our population of interest. Because of no known harm of high dose folic acid, the recommendation continues as 5 mg of folic acid for those at higher risk of NTDs.

The evidence was only available for those with history of NTDs and those at risk of preeclampsia so the committee agreed based on their expertise, the other groups who should be offered high dose of folic acid. No evidence was identified investigating high dose folic acid in pregnant women with pre-gestational type 1 or type 2 diabetes who are anticipating pregnancy or in the first 12 weeks of pregnancy, however, the committee were aware that pre-gestational diabetes is associated with increased risk of babies being born with NTDs or other congenital malformations. The committee agreed that the mechanism involves uncontrolled blood glucose which can lead to changes in methylation status in key genes including raised oxidative stress, mitochondria dysfunction and rates of apoptosis and cell death in neurodevelopment pathways. Because of the higher risk of NTDs in the diabetic population, the committee agreed that these women should be advised to take high dose folic acid.

No evidence was identified investigating high dose folic acid in pregnant women with sickle cell anaemia and thalassaemia, in pregnant women with epilepsy taking anti-epileptic medication or in women taking medication that affects the absorption of folic acid. Therefore, the committee made their recommendations based on their knowledge and experience. The committee were aware of groups of people that require a higher dose of folic acid. For

example, those with sickle cell anaemia are at an increased risk of folate deficiency due to haemolytic anaemia and therefore require a high dose to compensate for the increased demand for folate during pregnancy. The committee noted that those with thalassaemia may similarly have a greater risk of their baby developing neural tube defects. The committee also discussed those with epilepsy taking anti-epileptic medications and was aware that these medications interact with folate metabolism resulting in low levels of serum and red blood cell folate concentrations. The committee discussed other groups of people taking medication that interferes with folic acid absorption, such as those taking HIV medication. The committee agreed that a high dose should be given to these groups of people to reduce the risk of births with neural tube defects.

The committee agreed that since there is no evidence for 5 mg folic acid for women at greater risk of delivering a baby with a NTD, it is important to determine whether this dose can result in over-supplementation. Especially given the UK government decision from 2021 of mandatory fortification of white flour with folic acid. Therefore, the committee agreed to make a research recommendation on 5 mg folic acid per day in pregnant people with a high risk of NTDs. The committee also included pregnant people with a BMI of ≥25 kg/m^2 in the research recommendation. Pregnant people with a BMI of ≥25 kg/m^2 were excluded from this review, however appropriate folic acid dose for this group was included in evidence review B, but there was limited evidence. See Appendix K for more details.

There was some very low-quality evidence identified from 1 RCT that reported 4 mg of folic acid per day beyond the first trimester showed no important difference for pre-eclampsia in women at high risk of developing this condition compared to placebo. The committee were aware that this group are not currently prescribed high dose folic acid in clinical practice. The committee agreed with the evidence that high dose folic acid did not reduce the risk of pre-eclampsia and therefore made a recommendation in line with the evidence.

All available evidence was in those with single pregnancies. There was no evidence for women with multiple pregnancies, hence the committee did not make any specific recommendations for this group. The committee referred to the section on diet, lifestyle and nutritional supplements in the NICE guideline on Twin and triplet pregnancy, as this provides advice on nutritional supplements including folic acid for multiple pregnancies.

Cost effectiveness and resource use

No economic evidence was identified for this review question. Overall, the recommendations reflect current practice, so no resource implications are expected. The daily cost of the high dose 5 mg tablets (28 for £0.68) is slightly lower than the daily cost of the standard dose 400 microgram tablets (90 for £3.27). It is noted, however, that the 400 microgram tablets are available over the counter (and are usually bought over the counter), whereas the 5 mg tablets are available by prescription only (so, a person requiring the high dose tablets normally needs to pay the prescription charge of currently £9.90 pre-conception unless they are exempt, but the prescription is free during pregnancy). Offering the higher dose tablet to people who would benefit from it is expected to lead to important benefits and cost-savings resulting from prevention of babies born with neural tube defects.

Other factors the committee took into account

For this review question, the population in the evidence was women and no evidence was identified or reviewed for trans men or non-binary people. The protocol and literature searches were not designed to specifically look for evidence on trans men or non-binary people but they were also not excluded. However, there is a small chance evidence on them may not have been captured, if such evidence exists. In discussing the evidence, the committee considered whether the recommendations could apply to a broader population, and used gender inclusive language to promote equity, respect and effective communication with everyone. Healthcare professionals should use their clinical judgement when

implementing the recommendations, taking into account each person's circumstances, needs and preferences, and ensuring all people are treated with dignity and respect throughout their care.

Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.5 and 1.1.7 and the research recommendation on high-dose folic acid supplementation.

References – included studies

Effectiveness

Laurence 1981
Laurence, K M, James, N, Miller, M H et al. (1981) Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects. British medical journal (Clinical research ed.) 282(6275): 1509-11

MRC 1991
MRC (1991) Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet (London, England) 338(8760): 131-7

Wen 2018
Wen, Shi Wu, White, Ruth Rennicks, Rybak, Natalie et al. (2018) Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial. BMJ (Clinical research ed.) 362: k3478

Other

Wald, N.J., Morris, J.K. & Blakemore, C. (2018) Public health failure in the prevention of neural tube defects: time to abandon the tolerable upper intake level of folate. Public Health Rev 39(2)

Appendices

Appendix A Review protocols

Review protocol for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42022346779
Review title	High-dose folic acid supplementation before and during the first 12 weeks of pregnancy
Review question	Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?
Objective	To determine which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • CINAHLInternational HTA Database • Health Technology Assessment (HTA) database (last updated October 2016). Searches will be restricted by: • English language only • human studies only.

Field	Content
	Other searches: • inclusion lists of systematic reviews. The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Folic acid supplementation
Population	Women in the preconception stage trying to become pregnant or women during the first 12 weeks of a single or multiple pregnancy
Intervention	• High-dose folic acid supplementation (≥5 mg daily) In combination or not with other vitamins and minerals
Comparator	• Low-dose folic acid supplementation (<1 mg daily) • Medium-dose folic acid supplementation (≥1 to <5 mg daily) • Placebo • No intervention In combination or not with other vitamins and minerals

Types of study to be included	Include published full-text papers:
	• systematic reviews of RCTs
	• parallel RCTs
	• if insufficient parallel RCTs*:
	  ○ observational studies:
	  - systematic reviews of observational studies
	  - prospective cohort studies
	  - retrospective cohort studies

Field	Content
	- historically controlled studies. *Non-randomised studies will be considered for inclusion if insufficient RCT evidence is available for guideline decision making. Sufficiency will be judged taking into account factors including number/quality/sample size of RCTs, outcomes reported and availability of data from subgroups of interest. Non-randomised studies will only be included if they adjust for cofounding factors in the analysis. Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	Population: • women with a BMI ≥25kg/m^2. Setting: • countries other than high income countries (as defined by the OECD). *If any study or systematic review includes <1/3 of women with the above characteristics who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness.*
Context	The population of this guideline may overlap with the population of women included in other NICE guidelines (such as postnatal care, diabetes in pregnancy, antenatal care, intrapartum care, pregnancy and complex social factors or obesity prevention).
Primary outcomes (critical outcomes)	• Neural tube defects (NTDs) in the baby • Birthweight • Hypertensive disorders of pregnancy (pre-eclampsia and gestational hypertension).
Secondary outcomes (important outcomes)	• Red blood cell (RBC) (or serum if RBC is not reported) folate concentrations in the mother • Neurodevelopmental outcomes (dichotomous outcome, not continuous outcomes such as mean change in score):

Field	Content
	○ severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of mental development index [MDI] or psychomotor developmental index [PDI]) ○ moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84). • congenital heart defects • midline facial defects such as cleft lip or cleft palate. If there is a composite outcome that includes any of the outcomes above, the composite outcome will be reported and given priority over individually reported outcomes
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. Duplicate screening will not be undertaken for this question. Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs and quasi-RCTs • Cochrane ROBINS-I tool for non-randomised (clinical) controlled trials.

Field	Content
	The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled. The confidence in the findings across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group: http://www.gradeworkinggroup.org/ **Minimally important differences:** • NTDs, hypertensive disorders of pregnancy, neurodevelopmental outcomes, congenital heart defects, cleft palate: statistical significance • validated scales/continuous outcomes: published MIDs where available • all other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes; +/- 0.5x control group SD for continuous outcomes.
Analysis of subgroups	The following factors will be of interest in any meta-regression or subgroup analyses: • single versus multi-fetal pregnancies • women with a previous history of a pregnancy affected by a neural tube defect versus not • women taking antiseizure medications versus not • women taking antifolate medications versus not

Field	Content

	• women with diabetes (type 1 and type 2) versus not
	• women who started folic acid pre-conception versus not (specify timing if reported).
	
	If the evidence identifies additional groups which have not been listed here, these groups will be reported in the evidence.
	
	Evidence will be sub-grouped by the following only in the event that there is significant heterogeneity in outcomes:
	• deprived socioeconomic group
	• age <40 versus ≥40
	• women and parents with disabilities, including learning disabilities and other physical and mental health conditions
	• women going through assisted conception
	• religion and cultural considerations
	• ethnicity:
	  ○ White/White British
	  ○ Asian/Asian British
	  ○ Black/African/Caribbean/Black British
	  ○ Mixed/Multiple ethnic groups
	  ○ other ethnic group.
	• women who smoke versus not.
	
	Where evidence is stratified or sub-grouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.

<table>
<tr><th>Field</th><th>Content</th></tr>
<tr><td>Type and method of review</td><td>☒ Intervention
☐ Diagnostic
☐ Prognostic
☐ Qualitative
☐ Epidemiologic
☐ Service Delivery
☐ Other (please specify)</td></tr>
<tr><td>Language</td><td>English</td></tr>
<tr><td>Country</td><td>England</td></tr>
<tr><td>Anticipated or actual start date</td><td>14/07/2023</td></tr>
<tr><td>Anticipated completion date</td><td>22/11/2023</td></tr>
<tr><td>Stage of review at time of this submission</td><td>
<table>
<tr><th>Review stage</th><th>Started</th><th>Completed</th></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☒</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☒</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☒</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☒</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☒</td></tr>
</table>
</td></tr>
</table>

Field	Content
	Data analysis ☐ ☒
Named contact	**5a. Named contact** National Institute for Health and Care Excellence (NICE) **5b. Named contact e-mail** mandcnutrition@nice.org.uk **5c. Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE)
Review team members	From the National Institute for Health and Care Excellence (NICE): • senior Systematic Reviewer • systematic Reviewer.
Funding sources/sponsor	This systematic review is being completed by the National Institute for Health and Care Excellence (NICE).
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10191
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=346779
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

Field	Content
	notifying registered stakeholders of publication publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Folic acid, pregnancy, overweight, obesity
Details of existing review of same topic by same authors	Not applicable
Current review status	☐ Ongoing ☐ Completed but not published ☒ Completed and published ☐ Completed, published and being updated ☐ Discontinued
Additional information	None
Details of final publication	www.nice.org.uk

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; EPPI: Evidence for Policy & Practice Information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; m: metre; MID: minimally important difference; mg: milligrams; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; OECD: Organization for Economic Cooperation and Development; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation

Appendix B Literature search strategies

Literature search strategies for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Effectiveness searches

Database: Medline

Date of last search: 04/12/2023

#	Searches
1	exp Pregnancy/ or Pregnant Women/ or Prenatal Care/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	Preconception Care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	Folic Acid/ or Folic Acid Deficiency/
11	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
12	or/10-11
13	9 and 12
14	letter/
15	editorial/
16	news/
17	exp historical article/
18	Anecdotes as Topic/
19	comment/
20	case report/
21	(letter or comment*).ti.
22	or/14-21
23	randomized controlled trial/ or random*.ti,ab.
24	22 not 23
25	animals/ not humans/
26	exp Animals, Laboratory/
27	exp Animal Experimentation/
28	exp Models, Animal/
29	exp Rodentia/
30	(rat or rats or mouse or mice or rodent*).ti.
31	or/24-30
32	13 not 31
33	limit 32 to English language
34	randomized controlled trial.pt.
35	controlled clinical trial.pt.
36	pragmatic clinical trial.pt.
37	randomi#ed.ab.
38	placebo.ab.
39	drug therapy.fs.
40	randomly.ab.
41	trial.ab.
42	groups.ab.

#	Searches
43	or/34-42
44	Meta-Analysis/
45	Meta-Analysis as Topic/
46	(meta analy* or metanaly* or metaanaly*).ti,ab.
47	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
48	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50	(search* adj4 literature).ab.
51	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52	cochrane.jw.
53	or/44-52
54	33 and (43 or 53)
55	Observational Studies as Topic/
56	Observational Study/
57	Epidemiologic Studies/
58	exp Case-Control Studies/
59	exp Cohort Studies/
60	Cross-Sectional Studies/
61	Controlled Before-After Studies/
62	Historically Controlled Study/
63	Interrupted Time Series Analysis/
64	Comparative Study.pt.
65	case control$.tw.
66	case series.tw.
67	(cohort adj (study or studies)).tw.
68	cohort analy$.tw.
69	(follow up adj (study or studies)).tw.
70	(observational adj (study or studies)).tw.
71	longitudinal.tw.
72	prospective.tw.
73	retrospective.tw.
74	cross sectional.tw.
75	or/55-74
76	33 and 75
77	76 not 54
78	afghanistan/ or africa/ or africa, northern/ or africa, central/ or africa, eastern/ or "africa south of the sahara"/ or africa, southern/ or africa, western/ or albania/ or algeria/ or andorra/ or angola/ or "antigua and barbuda"/ or argentina/ or armenia/ or azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or "bosnia and herzegovina"/ or botswana/ or brazil/ or brunei/ or bulgaria/ or burkina faso/ or burundi/ or cabo verde/ or cambodia/ or cameroon/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cote d'ivoire/ or croatia/ or cuba/ or "democratic republic of the congo"/ or cyprus/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or egypt/ or el salvador/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or fiji/ or gabon/ or gambia/ or "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or independent state of samoa/ or exp india/ or indian ocean islands/ or indochina/ or indonesia/ or iran/ or iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libya/ or madagascar/ or malaysia/ or malawi/ or mali/ or malta/ or mauritania/ or mauritius/ or mekong valley/ or melanesia/ or micronesia/ or monaco/ or mongolia/ or montenegro/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nepal/ or nicaragua/ or niger/ or nigeria/ or oman/ or pakistan/ or palau/ or exp panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or qatar/ or "republic of belarus"/ or "republic of north macedonia"/ or romania/ or exp russia/ or rwanda/ or "saint kitts and nevis"/ or saint lucia/ or "saint vincent and the grenadines"/ or "sao tome and principe"/ or saudi arabia/ or serbia/ or sierra leone/ or senegal/ or seychelles/ or singapore/ or somalia/ or south africa/ or south sudan/ or sri lanka/ or sudan/ or suriname/ or syria/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or turkmenistan/ or uganda/ or ukraine/ or united arab emirates/ or uruguay/ or uzbekistan/ or vanuatu/ or venezuela/ or vietnam/ or west indies/ or yemen/ or zambia/ or zimbabwe/
79	"organisation for economic co-operation and development"/
80	australasia/ or exp australia/ or austria/ or baltic states/ or belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or exp denmark/ or estonia/ or europe/ or finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or exp japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or

#	Searches
	mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or portugal/ or exp "republic of korea"/ or "scandinavian and nordic countries"/ or slovakia/ or slovenia/ or spain/ or sweden/ or switzerland/ or turkey/ or exp united kingdom/ or exp united states/
81	european union/
82	developed countries/
83	or/79-82
84	78 not 83
85	54 not 84
86	77 not 84

Database: Embase

Date of last search: 04/12/2023

#	Searches
1	exp pregnancy/ or pregnant woman/ or prenatal care/ or prenatal period/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	prepregnancy care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	folic acid/ or folic acid deficiency/
11	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
12	or/10-11
13	9 and 12
14	letter.pt. or letter/
15	note.pt.
16	editorial.pt.
17	case report/ or case study/
18	(letter or comment*).ti.
19	or/14-18
20	randomized controlled trial/ or random*.ti,ab.
21	19 not 20
22	animal/ not human/
23	nonhuman/
24	exp Animal Experiment/
25	exp Experimental Animal/
26	animal model/
27	exp Rodent/
28	(rat or rats or mouse or mice or rodent*).ti.
29	or/21-28
30	13 not 29
31	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
32	30 not 31
33	limit 32 to English language
34	random*.ti,ab.
35	factorial*.ti,ab.
36	(crossover* or cross over*).ti,ab.
37	((doubl* or singl*) adj blind*).ti,ab.
38	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39	crossover procedure/

#	Searches
40	single blind procedure/
41	randomized controlled trial/
42	double blind procedure/
43	or/34-42
44	systematic review/
45	meta-analysis/
46	(meta analy* or metanaly* or metaanaly*).ti,ab.
47	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
48	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50	(search* adj4 literature).ab.
51	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
52	((pool* or combined) adj2 (data or trials or studies or results)).ab.
53	cochrane.jw.
54	or/44-53
55	33 and (43 or 54)
56	Clinical study/
57	Case control study/
58	Family study/
59	Longitudinal study/
60	Retrospective study/
61	comparative study/
62	Prospective study/
63	Randomized controlled trials/
64	62 not 63
65	Cohort analysis/
66	cohort analy$.tw.
67	(Cohort adj (study or studies)).tw.
68	(Case control$ adj (study or studies)).tw.
69	(follow up adj (study or studies)).tw.
70	(observational adj (study or studies)).tw.
71	(epidemiologic$ adj (study or studies)).tw.
72	(cross sectional adj (study or studies)).tw.
73	case series.tw.
74	prospective.tw.
75	retrospective.tw.
76	or/56-61,64-75
77	33 and 76
78	77 not 55
79	afghanistan/ or africa/ or "africa south of the sahara"/ or albania/ or algeria/ or andorra/ or angola/ or argentina/ or "antigua and barbuda"/ or armenia/ or exp azerbaijan/ or bahamas/ or bahrain/ or bangladesh/ or barbados/ or belarus/ or belize/ or benin/ or bhutan/ or bolivia/ or borneo/ or exp "bosnia and herzegovina"/ or botswana/ or exp brazil/ or brunei darussalam/ or bulgaria/ or burkina faso/ or burundi/ or cambodia/ or cameroon/ or cape verde/ or central africa/ or central african republic/ or chad/ or exp china/ or comoros/ or congo/ or cook islands/ or cote d'ivoire/ or croatia/ or cuba/ or cyprus/ or democratic republic congo/ or djibouti/ or dominica/ or dominican republic/ or ecuador/ or el salvador/ or egypt/ or equatorial guinea/ or eritrea/ or eswatini/ or ethiopia/ or exp "federated states of micronesia"/ or fiji/ or gabon/ or gambia/ or exp "georgia (republic)"/ or ghana/ or grenada/ or guatemala/ or guinea/ or guinea-bissau/ or guyana/ or haiti/ or honduras/ or exp india/ or exp indonesia/ or iran/ or exp iraq/ or jamaica/ or jordan/ or kazakhstan/ or kenya/ or kiribati/ or kosovo/ or kuwait/ or kyrgyzstan/ or laos/ or lebanon/ or liechtenstein/ or lesotho/ or liberia/ or libyan arab jamahiriya/ or madagascar/ or malawi/ or exp malaysia/ or maldives/ or mali/ or malta/ or mauritania/ or mauritius/ or melanesia/ or moldova/ or monaco/ or mongolia/ or "montenegro (republic)"/ or morocco/ or mozambique/ or myanmar/ or namibia/ or nauru/ or nepal/ or nicaragua/ or niger/ or nigeria/ or niue/ or north africa/ or oman/ or exp pakistan/ or palau/ or palestine/ or panama/ or papua new guinea/ or paraguay/ or peru/ or philippines/ or polynesia/ or qatar/ or "republic of north macedonia"/ or romania/ or exp russian federation/ or rwanda/ or sahel/ or "saint kitts and nevis"/ or "saint lucia"/ or "saint vincent and the grenadines"/ or saudi arabia/ or senegal/ or exp serbia/ or seychelles/ or sierra leone/ or singapore/ or "sao tome and principe"/ or solomon islands/ or exp somalia/ or south africa/ or south asia/ or south sudan/ or exp southeast asia/ or sri lanka/ or sudan/ or suriname/ or syrian arab republic/ or taiwan/ or tajikistan/ or tanzania/ or thailand/ or timor-leste/ or togo/ or tonga/ or "trinidad and tobago"/ or tunisia/ or

#	Searches
	turkmenistan/ or tuvalu/ or uganda/ or exp ukraine/ or exp united arab emirates/ or uruguay/ or exp uzbekistan/ or vanuatu/ or venezuela/ or viet nam/ or western sahara/ or yemen/ or zambia/ or zimbabwe/
80	exp "organisation for economic co-operation and development"/
81	exp australia/ or "australia and new zealand"/ or austria/ or baltic states/ or exp belgium/ or exp canada/ or chile/ or colombia/ or costa rica/ or czech republic/ or denmark/ or estonia/ or europe/ or exp finland/ or exp france/ or exp germany/ or greece/ or hungary/ or iceland/ or ireland/ or israel/ or exp italy/ or japan/ or korea/ or latvia/ or lithuania/ or luxembourg/ or exp mexico/ or netherlands/ or new zealand/ or north america/ or exp norway/ or poland/ or exp portugal/ or scandinavia/ or sweden/ or slovakia/ or slovenia/ or south korea/ or exp spain/ or switzerland/ or "Turkey (republic)"/ or exp united kingdom/ or exp united states/ or western europe/
82	european union/
83	developed country/
84	or/80-83
85	79 not 84
86	55 not 85
87	78 not 85

Database: Cochrane Database of Systematic Reviews Issue 12 of 12, December 2023 & Cochrane Central Register of Controlled Trials Issue 12 of 12, December 2023

Date of last search: 04/12/2023

#	Searches
#1	MeSH descriptor: [Pregnancy] explode all trees
#2	MeSH descriptor: [Pregnant Women] this term only
#3	MeSH descriptor: [Prenatal Care] this term only
#4	(antenatal* or ante NEXT natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre NEXT natal*):ti,ab,kw
#5	{OR #1-#4}
#6	MeSH descriptor: [Preconception Care] this term only
#7	(periconcept* or peri NEXT concept* or preconcept* or pre NEXT concept* or prepregnan* or pre NEXT pregnan*):ti,ab,kw
#8	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) near/3 (baby or babies or conceiving or pregnan* or conception* or conceive*)):ti,ab,kw
#9	(start* NEAR/2 family):ti,ab
#10	{OR #6-#9}
#11	#5 OR #10
#12	MeSH descriptor: [Folic Acid] this term only
#13	MeSH descriptor: [Folic Acid Deficiency] this term only
#14	(folic acid* or folate* or folacin or vitamin b9 or "vitamin b 9" or "vitamin m" or pteroylglutamic NEXT acid* or folvite):ti,ab,kw
#15	{OR #12-#14}
#16	#11 AND #15
#17	conference:pt or (clinicaltrials or trialsearch):so
#18	#16 NOT #17

Database: CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Date of last search: 04/12/2023

#	Searches
S1	(MH "Pregnancy+")
S2	(MH "Expectant Mothers")
S3	(MH "Prenatal Care")
S4	TI ((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*)) OR AB ((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))
S5	S1 OR S2 OR S3 OR S4
S6	(MH "Prepregnancy Care")
S7	TI ((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*)) OR AB ((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))

#	Searches
S8	TI (((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) N3 (baby or babies or conceiving or pregnan* or conception* or conceive*))) OR AB (((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) N3 (baby or babies or conceiving or pregnan* or conception* or conceive*)))
S9	TI (start* N2 family) OR AB (start* N2 family)
S10	S6 OR S7 OR S8 OR S9
S11	S5 OR S10
S12	(MH "Folic Acid") OR (MH "Folic Acid Deficiency")
S13	TI ((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite)) OR AB ((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite))
S14	S12 OR S13
S15	S11 AND S14
S16	S11 AND S14
S17	S11 AND S14

Database: Epistemonikos

Date of last search: 04/12/2023

#	Searches
1	title:((pregnan* OR antenatal OR prenatal OR periconcept* OR preconcept* OR prepregnan*)) or abstract:((pregnan* OR antenatal OR prenatal OR periconcept* OR preconcept* OR prepregnan*))
2	title:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite)) OR abstract:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite)
3	#1 and #2 [Filters: classification=systematic-review, cochrane=missing, protocol=no]

Economic searches

Database: Medline

Date of last search: 04/12/2023

#	Searches
1	exp Pregnancy/ or Pregnant Women/ or Prenatal Care/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	Preconception Care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	Folic Acid/ or Folic Acid Deficiency/
11	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
12	or/10-11
13	9 and 12
14	letter/
15	editorial/
16	news/
17	exp historical article/
18	Anecdotes as Topic/
19	comment/
20	case reports/
21	(letter or comment*).ti.
22	or/14-21
23	randomized controlled trial/ or random*.ti,ab.

#	Searches
24	22 not 23
25	animals/ not humans/
26	exp Animals, Laboratory/
27	exp Animal Experimentation/
28	exp Models, Animal/
29	exp Rodentia/
30	(rat or rats or mouse or mice or rodent*).ti.
31	or/24-30
32	13 not 31
33	limit 32 to English language
34	Economics/
35	Value of life/
36	exp "Costs and Cost Analysis"/
37	exp Economics, Hospital/
38	exp Economics, Medical/
39	exp Resource Allocation/
40	Economics, Nursing/
41	Economics, Pharmaceutical/
42	exp "Fees and Charges"/
43	exp Budgets/
44	budget*.ti,ab.
45	cost*.ti,ab.
46	(economic* or pharmaco?economic*).ti,ab.
47	(price* or pricing*).ti,ab.
48	(financ* or fee or fees or expenditure* or saving*).ti,ab.
49	(value adj2 (money or monetary)).ti,ab.
50	resourc* allocat*.ti,ab.
51	(fund or funds or funding* or funded).ti,ab.
52	(ration or rations or rationing* or rationed).ti,ab.
53	ec.fs.
54	or/34-53
55	exp models, economic/
56	*Models, Theoretical/
57	*Models, Organizational/
58	markov chains/
59	monte carlo method/
60	exp Decision Theory/
61	(markov* or monte carlo).ti,ab.
62	econom* model*.ti,ab.
63	(decision* adj2 (tree* or analy* or model*)).ti,ab.
64	or/55-63
65	quality-adjusted life years/
66	sickness impact profile/
67	(quality adj2 (wellbeing or well being)).ti,ab.
68	sickness impact profile.ti,ab.
69	disability adjusted life.ti,ab.
70	(qal* or qtime* or qwb* or daly*).ti,ab.
71	(euroqol* or eq5d* or eq 5*).ti,ab.
72	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
73	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
74	(hui or hui1 or hui2 or hui3).ti,ab.
75	(health* year* equivalent* or hye or hyes).ti,ab.
76	discrete choice*.ti,ab.

#	Searches
77	rosser.ti,ab.
78	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
79	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
80	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
81	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
82	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
83	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
84	or/65-83
85	33 and (54 or 64 or 84)

Database: Embase

Date of last search: 04/12/2023

#	Searches
1	exp pregnancy/ or pregnant woman/ or prenatal care/ or prenatal period/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,kf.
3	1 or 2
4	prepregnancy care/
5	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,kf.
6	((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)).ti,ab,kf.
7	(start* adj2 family).ti,ab.
8	or/4-7
9	3 or 8
10	folic acid/ or folic acid deficiency/
11	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
12	or/10-11
13	9 and 12
14	letter.pt. or letter/
15	note.pt.
16	editorial.pt.
17	case report/ or case study/
18	(letter or comment*).ti.
19	or/14-18
20	randomized controlled trial/ or random*.ti,ab.
21	19 not 20
22	animal/ not human/
23	nonhuman/
24	exp Animal Experiment/
25	exp Experimental Animal/
26	animal model/
27	exp Rodent/
28	(rat or rats or mouse or mice or rodent*).ti.
29	or/21-28
30	13 not 29
31	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
32	30 not 31
33	limit 32 to English language
34	health economics/
35	exp economic evaluation/
36	exp health care cost/
37	exp fee/
38	budget/
39	funding/

#	Searches
40	resource allocation/
41	budget*.ti,ab.
42	cost*.ti,ab.
43	(economic* or pharmaco?economic*).ti,ab.
44	(price* or pricing*).ti,ab.
45	(financ* or fee or fees or expenditure* or saving*).ti,ab.
46	(value adj2 (money or monetary)).ti,ab.
47	resourc* allocat*.ti,ab.
48	(fund or funds or funding* or funded).ti,ab.
49	(ration or rations or rationing* or rationed).ti,ab.
50	or/34-49
51	statistical model/
52	exp economic aspect/
53	51 and 52
54	*theoretical model/
55	*nonbiological model/
56	stochastic model/
57	decision theory/
58	decision tree/
59	monte carlo method/
60	(markov* or monte carlo).ti,ab.
61	econom* model*.ti,ab.
62	(decision* adj2 (tree* or analy* or model*)).ti,ab.
63	or/53-62
64	quality adjusted life year/
65	"quality of life index"/
66	short form 12/ or short form 20/ or short form 36/ or short form 8/
67	sickness impact profile/
68	(quality adj2 (wellbeing or well being)).ti,ab.
69	sickness impact profile.ti,ab.
70	disability adjusted life.ti,ab.
71	(qal* or qtime* or qwb* or daly*).ti,ab.
72	(qal* or qtime* or qwb* or daly*).ti,ab.
73	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
74	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
75	(hui or hui1 or hui2 or hui3).ti,ab.
76	(health* year* equivalent* or hye or hyes).ti,ab.
77	discrete choice*.ti,ab.
78	rosser.ti,ab.
79	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
80	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
81	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
82	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
83	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
84	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
85	or/64-84
86	33 and (50 or 63 or 85)

Database: INAHTA HTA

Date of last search: 04/12/2023

#	Searches
1	"Pregnancy"[mhe]

#	Searches
2	"Pregnant Women"[mh]
3	"Prenatal Care"[mh]
4	((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[Title] OR ((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[abs]
5	#4 OR #3 OR #2 OR #1
6	"Preconception Care"[mh]
7	((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))[Title] OR ((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))[abs]
8	(((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) AND (baby or babies or conceiving or pregnan* or conception* or conceive*)))[Title] OR (((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) AND (baby or babies or conceiving or pregnan* or conception* or conceive*)))[abs]
9	((start* AND family))[Title] OR ((start* AND family))[abs]
10	#9 OR #8 OR #7 OR #6
11	#10 OR #5
12	"Folic Acid"[mh]
13	"Folic Acid Deficiency"[mh]
14	((folic acid* or folate* or folacin or "vitamin b9" or "vitamin b 9" or "vitamin m" or "pteroylglutamic acid*" or folvite))[Title] OR ((folic acid* or folate* or folacin or "vitamin b9" or "vitamin b 9" or "vitamin m" or "pteroylglutamic acid*" or folvite))[abs]
15	#14 OR #13 OR #12
16	#15 AND #11 Limit by English language

Database: CRD HTA (last updated October 2016)

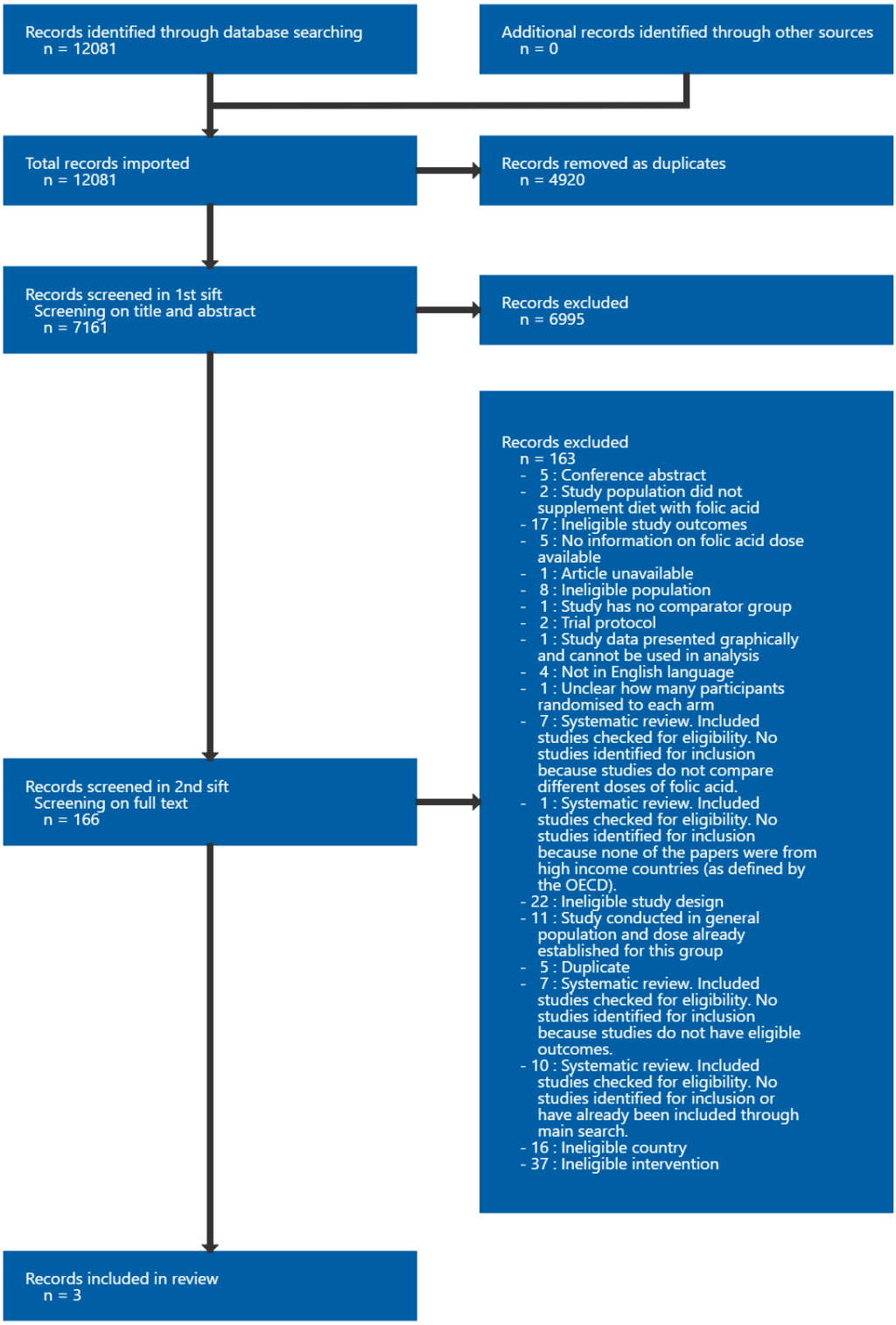
Date of last search: 20/07/2022

#	Searches
1	MeSH DESCRIPTOR pregnancy EXPLODE ALL TREES IN HTA
2	MeSH DESCRIPTOR pregnant women IN HTA
3	MeSH DESCRIPTOR prenatal care IN HTA
4	(((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
5	#1 OR #2 OR #3 OR #4
6	MeSH DESCRIPTOR preconception care IN HTA
7	(((periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
8	(((((before or plan* or intend* or intention* or wish* or desir* or want* or prior or prepar* or try* or becom* or get* or start*) adj3 (baby or babies or conceiving or pregnan* or conception* or conceive*)))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
9	(((start* adj2 family))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
10	#6 OR #7 OR #8 OR #9
11	#5 OR #10
12	MeSH DESCRIPTOR folic acid IN HTA
13	MeSH DESCRIPTOR folic acid deficiency IN HTA
14	(((folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite))) and (Project record:ZDT OR Full publication record:ZDT) IN HTA
15	#12 OR #13 OR #14
16	#11 AND #15

Appendix C Effectiveness evidence study selection

Study selection for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Figure 1: Effectiveness evidence study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Table 5: Evidence tables

Laurence, 1981

Bibliographic Reference	Laurence, K M; James, N; Miller, M H; Tennant, G B; Campbell, H; Double-blind randomised controlled trial of folate treatment before conception to prevent recurrence of neural-tube defects.; British medical journal (Clinical research ed.); 1981; vol. 282 (no. 6275); 1509-11

Study details

Country/ies where study was carried out	UK
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• History of birth with NTDs • Under 35 years
Exclusion criteria	Not reported
Patient characteristics	Not reported
Intervention(s)/control	Intervention: 4mg folic acid* Placebo *2x2mg tablets per day Taken from the time contraception stopped until birth
Duration of follow-up	At birth

Sources of funding	Not industry funded
Sample size	N=111 Intervention: n=60 Placebo: n=51
Other information	Subgroup in analysis: risk of preeclampsia or history of births with NTDs

mg: milligrams; n: number of participants; NTDs: neural tube defects

Study arms

4mg folic acid/day (n = 60)

Placebo (n = 51)

Outcomes

Outcome	**4mg folic acid/day, n = 60**	**Placebo, n = 51**
Neural tube defects measured at birth Number for intervention is combined for compliers and non-compliers No of events	n = 2; % = 1.2	n = 4; % = 2.04
Red blood cell folate concentration at birth Mean for intervention arm is combined for compliers and non-compliers Mean (SD) (µg/l red blood cells)	609 (218)	278 (16)

mg: milligrams; n: number of participants; SD: standard deviation

Critical appraisal - Cochrane Risk of Bias tool v2.0 for RCTs

Section	**Question**	**Answer**
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No study protocol reported)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to have some concerns of bias in one domain)*
Overall bias and Directness	Overall Directness	Directly applicable *(Study selected pregnant women with history of births with NTDs)*
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of bias in variation across outcomes

NTDs: neural tube defects; RCT: randomised controlled trial.

MRC, 1991

Bibliographic Reference	MRC; Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group.; Lancet (London, England); 1991; vol. 338 (no. 8760); 131-7

Study details

Country/ies where study was carried out	UK, Hungary, Australia, Israel, Canada, Russia, France
Study type	Randomised controlled trial (RCT)
Study dates	Not reported
Inclusion criteria	• Those with a history of a pregnancy with NTDs • Planning another pregnancy • Not taking vitamin supplements
Exclusion criteria	• Women with epilepsy
Patient characteristics	**Age in years, mean** (SD: NR) Group A (4mg folic acid): 27 Group B (4mg folic acid + multivitamin): 27.4 Group C (placebo): 26.8 **Maternal BMI** – NR **Livebirths in previous pregnancies, mean** Group A (4mg folic acid): 0.88 Group B (4mg folic acid + multivitamin): 0.94 Group C (placebo): 0.91 **Mean number of previous NTD pregnancies** Group A (4mg folic acid): 1.03

	Group B (4mg folic acid + multivitamin): 1.04 Group C (placebo): 1.01
Intervention(s)/control	Group A: 4mg folic acid Group B: 4mg folic acid + multivitamin Group C: Placebo (contains dried ferrous sulphate (120mg) and di-calcium phosphate (240mg) *1 capsule daily from date of randomisation until 12 weeks gestational age
Duration of follow-up	12 weeks of pregnancy
Sources of funding	Not industry funded
Sample size	N=893 Group A: n=298 Group B: n=295 Group C: n=300
Other information	Multivitamin composition: vitamin A 4000 IU, D 400 IU, Bl 1-5 mg, B2 1.5 mg, B6 10 mg, C 40 mg, and nicotinamide 15 mg. Subgroup in analysis: risk of preeclampsia or history of births with NTDs

BMI: body mass index; IU: international units; mg: milligrams; NR: not reported; NTDs: neural tube defects; SD: standard deviation

Study arms

Folic acid 4mg/day (n = 298)

Folic acid 4mg + multivitamins/day (n = 295)

Placebo (n = 300)

Outcomes

Outcome	Folic acid 4mg/day, n = 298	Folic acid 4mg + multivitamins/day, n = 295	Placebo, n = 300
Neural tube defects measured at 12 weeks of pregnancy No of events	n = 2; % = 0.67	n = 4; % = 1.4	n = 13; % = 4.3

mg: milligrams; n: number of participants

Critical appraisal - Cochrane Risk of Bias tool v2.0 for RCTs

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	High *(Outcome data were available for 64% of randomised participants. There is no evidence that the result was not biased by missing outcome data. Missingness in the outcome could depend on its true value, however this is not likely.)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(No study protocol reported)*

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to raise some concerns in one domain and high risk of bias in one domain)*
Overall bias and Directness	Overall Directness	Directly applicable *(Study selected pregnant women with history of births with NTDs)*
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of bias in variation across outcomes

NTDs: neural tube defects; RCT: randomised controlled trial.

Wen, 2018

Bibliographic Reference	Wen, Shi Wu; White, Ruth Rennicks; Rybak, Natalie; Gaudet, Laura M; Robson, Stephen; Hague, William; Simms-Stewart, Donnette; Carroli, Guillermo; Smith, Graeme; Fraser, William D; Wells, George; Davidge, Sandra T; Kingdom, John; Coyle, Doug; Fergusson, Dean; Corsi, Daniel J; Champagne, Josee; Sabri, Elham; Ramsay, Tim; Mol, Ben Willem J; Oudijk, Martijn A; Walker, Mark C; FACT Collaborating, Group; Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (FACT): double blind, phase III, randomised controlled, international, multicentre trial.; BMJ (Clinical research ed.); 2018; vol. 362; k3478

Study details

Country/ies where study was carried out	Canada, Argentina, Australia, Jamaica, UK
Study type	Randomised controlled trial (RCT)
Study dates	April 2011 to November 2015
Inclusion criteria	• 8-16 gestational weeks • Confirmed viable fetus • Risk factor for pre-eclampsia (pre-existing hypertension, prepregnancy diabetes (type 1 or 2), twin pregnancy, history of pre-eclampsia during pregnancy, BMI >=35 kg/m^2)
Exclusion criteria	• Known fetal anomaly or fetal death • History of maternal medical complications

	• Epilepsy • Cancer • Current use of folic acid antagonists • Substance misuse • Hypersensitivity to folic acid • Multiple pregnancy • Previous participation in current trial • History or presence of a disease or condition that would preclude use of high dose folic acid
Patient characteristics	**Maternal age in years, n (%)** Intervention: <20- 10 (0.8) 20-29- 439 (35.8) 30-34- 411 (33.5) ≥35- 367 (29.9) Age in years, mean (SD): 31 (5.4) Placebo: <20- 10 (0.8) 20-29- 447 (36.2) 30-34- 441 (35.7) ≥35- 338 (27.3)

	Age in years, mean (SD): 31 (5.4) Pregnancy BMI, mean (SD) Intervention: 34 (8.6) Control: 34 (13) **BMI ≥35, n (%)** Intervention: 606 (49.4) Control: 656 (53.1) Parity, n (%) Intervention: 0 - 413 (33.7) 1 - 498 (40.6) ≥2 - 316 (25.7) Control: 0 - 420 (34.0) 1 - 499 (40.4) ≥2 - 317 (25.6) **History of pre-eclampsia, n (%)**

	Intervention: 308 (25.1) Control: 303 (24.5) **Chronic hypertension, n (%)** Intervention: 203 (16.5) Control: 241 (19.5) **Type 1 diabetes, n (%)** Intervention: 84 (6.8) Control: 72 (5.8) **Type 2 diabetes, n (%)** Intervention: 98 (8.0) Control: 84 (6.8) **Twin pregnancy, n (%)** Intervention: 233 (19.0) Control: 229 (18.5) **Maternal ethnicity, n (%)** Intervention: Native/Aboriginal 35 (2.85)

	White 970 (79.0) Black 93 (7.6) Asian 45 (3.7) Latino/Hispanic 31 (2.5) Indian/South Asian 45 (3.7) Declined to answer 8 (0.65) Control: Native/Aboriginal 24 (1.94) White 987 (79.8) Black 107 (8.7) Asian 50 (4.05) Latino/Hispanic 22 (1.8) Indian/South Asian 36 (2.9) Declined to answer 10 (0.8) **Smoking during pregnancy, n (%)** Intervention: Yes 98 (8.0)

	No 1046 (85.2) Quit during pregnancy 83 (6.8) Control: Yes 95 (7.7) No 1035 (83.7) Quit during pregnancy 106 (8.6)
Intervention(s)/control	Intervention: 4mg folic acid (4x1mg tablets daily) Control: Placebo Taken from 8 to 16 weeks gestational age until birth. *Participants continued taking vitamins or folic acid supplements (up to 1.1 mg of folic acid).
Duration of follow-up	42 days post-partum
Sources of funding	Not industry funded
Sample size	N=2301 Intervention: n=1144 Control: n=1157
Other information	Participants who took folic acid supplementation additional to intervention: Folic acid supplementation (includes multivitamin containing folic acid) at randomisation Intervention: 989 (80.6) Control: 1016 (82.2)

	Supplementation of high dose (≥4.0 mg/d folic acid) at randomisation Intervention: 346 (28.2) Control: 335 (27.1) Subgroup in analysis: risk of preeclampsia or history of births with NTDs

BMI: body mass index; d: day; kg: kilogram; m: metre; mg: milligrams; n: number of participants; SD: standard deviation

Study arms

4mg folic acid (n = 1144)

Placebo (n = 1157)

Outcomes

Outcome	4mg folic acid, n = 1144	Placebo, n = 1157
Preeclampsia measured at 42 days post-partum No of events	n = 24; % = 2.1	n = 16; % = 1.4

n: number of participants; mg: milligrams

Critical appraisal - Cochrane Risk of Bias tool v2.0 for RCTs

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Participants could continue taking prenatal vitamins or low dose folic acid supplements (up to 1.1 mg of folic acid).)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns one domain)*
Overall bias and Directness	Overall Directness	Directly applicable *(Study selected pregnant women at high risk of developing pre-eclampsia)*
Overall bias and Directness	Risk of bias variation across outcomes	Low risk of bias in variation across outcomes

mg: milligrams; RCT: randomised controlled trial.

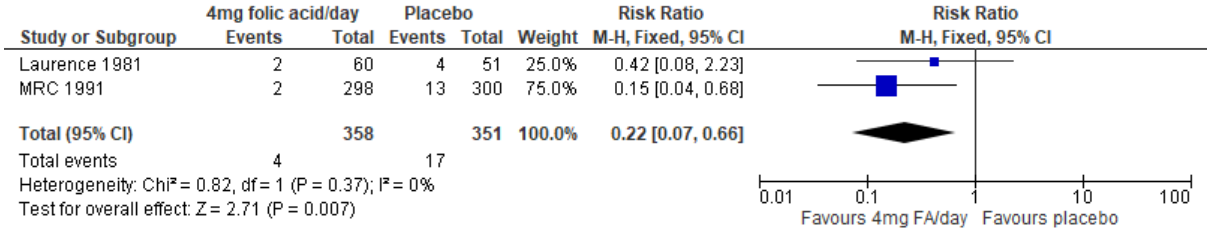
Appendix E Forest plots

Forest plots for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

This section includes forest plots only for outcomes that are meta-analysed. Outcomes from single studies are not presented here; the quality assessment for such outcomes is provided in the GRADE profiles in appendix F.

Comparison between folic acid supplementation 4mg/day and placebo in women with a history of births with neural tube defects (NTDs)

Figure 2: Neural tube defects (follow-up: at 12 weeks of pregnancy and birth)



CI: confidence interval; df: degrees of freedom; FA: folic acid; mg: milligrams; MRC: Medical Research Council; NTDs: neural tube defects

Appendix F GRADE tables

GRADE tables for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Table 6: Evidence profile for comparison between folic acid supplementation 4mg/day and placebo in women with a history of births with neural tube defects (NTDs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4mg folic acid/day	Placebo	Relative (95% CI)	Absolute		
Neural tube defects (follow-up: at 12 weeks of pregnancy and birth)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	4/358 (1.1%)	17/351 (4.9%)	RR 0.22 (0.07 to 0.65)	38 fewer per 1000 (from 17 fewer to 46 fewer)	LOW **IMP. BENEFIT**	CRITICAL
Red blood cell folate concentration (µg/l red blood cells) (Better indicated by higher values) (follow-up: at birth)												
1 Laurence 1981	randomised trials	serious[2]	no serious inconsistency	serious[3]	no serious imprecision	none	60	51	-	MD 331 higher (275.66 to 386.34 higher)	LOW **IMP. BENEFIT**	IMPORTANT

CI: confidence interval; MD: mean difference; mg: milligrams; RR: risk ratio

[1] See corresponding forest plot in appendix E for studies contributing to this outcome

[2] Serious risk of bias in the evidence contributing to the outcome as per RoB 2

[3] Intervention is indirect as folic acid 4 mg/day dose was used in the study. Did not include of high dose folic acid supplements (≥5 mg daily) as per protocol.

Table 7: Evidence profile for comparison between folic acid supplementation 4mg/day + multivitamin and placebo for women with a history of births with neural tube defects (NTDs)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4mg folic acid/day + multivitamin	Placebo	Relative (95% CI)	Absolute		
Neural tube defects (follow-up: at 12 weeks of pregnancy)												
1 MRC 1991	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[2]	none	4/295 (1.4%)	13/300 (4.3%)	RR 0.31 (0.10 to 0.95)	30 fewer per 1000 (from 2 fewer to 39 fewer)	VERY LOW **IMP. BENEFIT**	CRITICAL

CI: confidence interval; mg: milligrams; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcome as per RoB 2

[2] Intervention is indirect as folic acid 4 mg/day dose was used in the study. Did not include of high dose folic acid supplements (≥5 mg daily) as per protocol.

[3] Statistical significance was used to assess clinical importance. Imprecision was based on total number of events. <150 events.

Table 8: Evidence profile for comparison between folic acid supplementation 4mg/day and placebo in women at high risk of preeclampsia

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	4mg folic acid/day + multivitamin	Placebo	Relative (95% CI)	Absolute		
Severe pre-eclampsia (follow-up: at 42 days postpartum)												
1 Wen 2018	randomised trials	serious[1]	no serious inconsistency	very serious[2]	very serious[3]	none	24/1144 (2.1%)	16/1157 (1.4%)	RR 1.52 (0.81 to 2.84)	7 more per 1000 (from 3 fewer to 25 more)	VERY LOW **NO IMP. DIFF.**	CRITICAL

CI: confidence interval; mg: milligrams; RR: risk ratio

[1] Serious risk of bias in the evidence contributing to the outcome as per RoB 2

[2] Population and intervention are indirect due to >33% of population has a BMI>=35kg/m^2. Intervention is indirect as folic acid 4 mg/day dose was used in the study. Did not include of high dose folic acid supplements (≥5 mg daily) as per protocol.

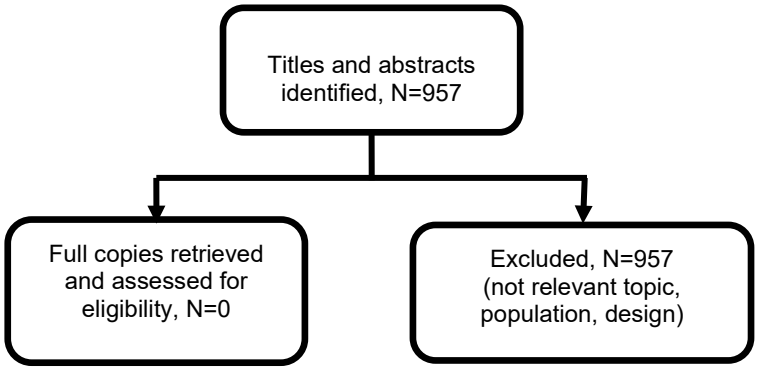
[3] Statistical significance was used to assess clinical importance. Imprecision was based on total number of events. <150 events.

Appendix G Economic evidence study selection

Study selection for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

No economic evidence was identified which was applicable to this review question.

Figure 3. Flow diagram of selection process for economic evaluations



Appendix H Economic evidence tables

Economic evidence tables for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

No evidence was identified which was applicable to this review question.

Appendix I Economic model

Economic model for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

No economic analysis was conducted for this review question.

Appendix J Excluded studies

Excluded studies for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Excluded effectiveness studies

Table 9: Excluded studies and reasons for their exclusion

Study	Code [Reason]
Ala, Syed H; Husain, Samia; Husain, Saba (2021) Reasons for presenting to antenatal care clinics in a sample of Pakistani women and their knowledge of WHO antenatal care package. European journal of midwifery 5: 43	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Ali Khan, R.E., Ahmad, T.I., Noreen, S. et al. (2020) Factors associated with the quality of Antenatal Care (ANC) services use in Bahawalpur. Journal of the Pakistan Medical Association 70(12b): 2457-2459	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Alvestad, Silje, Nilsen Husebye, Elisabeth Synnove, Christensen, Jakob et al. (2022) Folic Acid and Risk of Preterm Birth, Preeclampsia and Fetal Growth Restriction Among Women With Epilepsy: A Prospective Cohort Study. Neurology	- Ineligible intervention *Does not compare different doses of folic acid*
Avnon, Tomer, Anbar, Ronit, Lavie, Inbar et al. (2020) Does vegan diet influence umbilical cord vitamin B12, folate, and ferritin levels?. Archives of gynecology and obstetrics 301(6): 1417-1422	- Study population did not supplement diet with folic acid *Participants were analysed according to diet (for example, vegan diet, vegetarian diet, and so on)*
Bakker, Rachel, Timmermans, Sarah, Steegers, Eric A P et al. (2011) Folic acid supplements modify the adverse effects of maternal smoking on fetal growth and neonatal complications. The Journal of nutrition 141(12): 2172-9	- Ineligible intervention *Folic acid dosage of 0.4–0.5 mg/d. Prospective cohort study.*
Baumslag, N; Edelstein, T; Metz, J (1970) Reduction of incidence of prematurity by folic acid supplementation in pregnancy. British medical journal 1(5687): 16-7	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in South Africa.*
Baxter, J.-A.B., Wasan, Y., Soofi, S.B. et al. (2018) Effect of life skills building education and micronutrient supplements provided from preconception versus the standard of care on low birth weight births among adolescent and	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*

Study	Code [Reason]
young Pakistani women (15-24 years): A prospective, population-based cluster-randomized trial. Reproductive Health 15(1): 104	
Bermeo-Ovalle, A. (2020) Think Beyond Malformations: The Case for Periconceptional Folate in Women With Epilepsy. Epilepsy Currents 20(4): 202-204	- Ineligible study design *Narrative commentary*
Betts, T and Fox, C (1999) Proactive pre-conception counselling for women with epilepsy-is it effective?. Seizure 8(6): 322-7	- Ineligible study design *Retrospective study*
Bezerra Espinola, Maria Salome; Bilotta, Gabriele; Aragona, Cesare (2021) Positive effect of a new supplementation of vitamin D3 with myo-inositol, folic acid and melatonin on IVF outcomes: a prospective randomized and controlled pilot study. Gynecological endocrinology : the official journal of the International Society of Gynecological Endocrinology 37(3): 251-254	- Ineligible intervention *Study assesses effects of vitamin D3 on IVF outcomes*
Bhutta, Zulfiqar A, Imdad, Aamer, Ramakrishnan, Usha et al. (2012) Is it time to replace iron folate supplements in pregnancy with multiple micronutrients?. Paediatric and perinatal epidemiology 26suppl1: 27-35	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Systematic review included studies from low-middle income countries only.*
Bortolus, Renata, Blom, Fenneke, Filippini, Francesca et al. (2014) Prevention of congenital malformations and other adverse pregnancy outcomes with 4.0 mg of folic acid: community-based randomized clinical trial in Italy and the Netherlands. BMC pregnancy and childbirth 14: 166	- Trial protocol
Bortolus, Renata, Filippini, Francesca, Cipriani, Sonia et al. (2021) Efficacy of 4.0 mg versus 0.4 mg Folic Acid Supplementation on the Reproductive Outcomes: A Randomized Controlled Trial. Nutrients 13(12)	- Study conducted in general population and dose already established for this group *Study investigated 4 milligrams of folic acid*
Bower, C (1994) Epilepsy in pregnancy: neural tube defects and folate. The Medical journal of Australia 160(2): 56-7	- Ineligible study design *Narrative. Published letter/comment on another article*
Bramswig, Susanne, Prinz-Langenohl, Reinhild, Lamers, Yvonne et al. (2009) Supplementation	- Study conducted in general population and dose already established for this group

Study	Code [Reason]
with a multivitamin containing 800 microg of folic acid shortens the time to reach the preventive red blood cell folate concentration in healthy women. International journal for vitamin and nutrition research. Internationale Zeitschrift fur Vitamin- und Ernahrungsforschung. Journal international de vitaminologie et de nutrition 79(2): 61-70	*Study investigated 800 micrograms of folic acid*
Brieger, Katharine K, Bakulski, Kelly M, Pearce, Celeste L et al. (2022) The Association of Prenatal Vitamins and Folic Acid Supplement Intake with Odds of Autism Spectrum Disorder in a High-Risk Sibling Cohort, the Early Autism Risk Longitudinal Investigation (EARLI). Journal of autism and developmental disorders 52(6): 2801-2811	- Ineligible study design *Prospective cohort study*
Brough, L, Rees, G A, Crawford, M A et al. (2009) Social and ethnic differences in folic acid use preconception and during early pregnancy in the UK: effect on maternal folate status. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association 22(2): 100-7	- Ineligible study outcomes *Study reports on number of women taking folic acid supplements*
Brough, Louise, Rees, Gail A, Crawford, Michael A et al. (2010) Effect of multiple-micronutrient supplementation on maternal nutrient status, infant birth weight and gestational age at birth in a low-income, multi-ethnic population. The British journal of nutrition 104(3): 437-45	- Ineligible comparison *Compared low dose folic supplement (400µg folic acid in multivitamin "Pregnacare") vs placebo.*
Bukowski, Radek, Malone, Fergal D, Porter, Flint T et al. (2009) Preconceptional folate supplementation and the risk of spontaneous preterm birth: a cohort study. PLoS medicine 6(5): e1000061	- Ineligible study design *Prospective cohort study*
Busby, A., Abramsky, L., Dolk, H. et al. (2005) Preventing neural tube defects in Europe: Population based study. British Medical Journal 330(7491): 574-575	- Ineligible study design *Narrative commentary*
Butler, E B (1968) Effect of iron and folic acid on red cell and plasma volume in pregnancy. The Journal of obstetrics and gynaecology of the British Commonwealth 75(5): 497-510	- Ineligible study outcomes *Study assessed haemoglobin levels during pregnancy*
Butler, EB (1968) The effect of iron and folic acid on red cell and plasma volume in pregnancy. Journal of obstetrics and	- Duplicate

Study	Code [Reason]
gynaecology of the british commonwealth 75: 497-510	
Carretti, N, Eremita, G A, Porcelli, B et al. (1994) Pattern of vitamin B12 and folic acid during pregnancy. Gynecologic and obstetric investigation 38(2): 78-81	- Ineligible intervention *Study investigated folate/vitamin B12 concentrations and gestational age/levels of haemoglobin*
Castren, O, Levanto, A, Rauramo, L et al. (1968) Preventive iron and folic acid therapy in pregnancy. Annales chirurgiae et gynaecologiae Fenniae 57(3): 382-6	- Ineligible intervention *Study does not compare different doses of folic acid*
Castro, Kamila, Klein, Luciana da Silveira, Baronio, Diego et al. (2016) Folic acid and autism: What do we know?. Nutritional neuroscience 19(7): 310-7	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not compare different doses of folic acid.
Catena, Andres, Munoz-Machicao, J Angela, Torres-Espinola, Francisco J et al. (2016) Folate and long-chain polyunsaturated fatty acid supplementation during pregnancy has long-term effects on the attention system of 8.5-y-old offspring: a randomized controlled trial. The American journal of clinical nutrition 103(1): 115-27	- Ineligible intervention *Study assesses effect of fish oil and folate supplementation on children's neurocognitive development*
Catov, J.M., Bodnar, L.M., Olsen, J. et al. (2011) Periconceptional multivitamin use and risk of preterm or small-for-gestational-age Births in the Danish National birth cohort. American Journal of Clinical Nutrition 94(3): 906-912	- Ineligible intervention *Intervention compares timing of folic acid rather than dose*
Catov, Janet M, Bodnar, Lisa M, Ness, Roberta B et al. (2007) Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. American journal of epidemiology 166(3): 296-303	- Ineligible intervention *No information on dose reported*
Charles, Deborah H M, Ness, Andy R, Campbell, Doris et al. (2005) Folic acid supplements in pregnancy and birth outcome: re-analysis of a large randomised controlled trial and update of Cochrane review. Paediatric and perinatal epidemiology 19(2): 112-24	- Study conducted in general population and dose already established for this group *Study investigated 200 micrograms and 5 milligrams of folic acid*
Cheng, Zhengpei, Gu, Rui, Lian, Zenglin et al. (2022) Evaluation of the association between maternal folic acid supplementation and the risk of congenital heart disease: a systematic review and meta-analysis. Nutrition journal 21(1): 20	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not compare different doses of folic acid.

Study	Code [Reason]
Chiaffarino, F, Ascone, GB, Bortolus, R et al. (2010) [Effects of folic acid supplementation on pregnancy outcomes: a review of randomized clinical trials]. Minerva ginecologica 62(4): 293-301	- Not in English language
Chisholm, M (1966) A controlled clinical trial of prophylactic folic acid and iron in pregnancy. Journal of obstetrics and gynaecology of the British Commonwealth 73: 191-196	- Ineligible intervention *Study assesses relationship between iron/folic acid and anaemia*
Christian, P, Shahid, F, Rizvi, A et al. (2009) Treatment response to standard of care for severe anemia in pregnant women and effect of multivitamins and enhanced anthelminthics. American journal of clinical nutrition 89(3): 853-861	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Cochrane, K.M., Elango, R., Devlin, A.M. et al. (2023) Supplementation with (6 S)-5-methyltetrahydrofolic acid appears as effective as folic acid in maintaining maternal folate status while reducing unmetabolized folic acid in maternal plasma: A randomized trial of pregnant women in Canada. British Journal of Nutrition	- Study conducted in general population and dose already established for this group *Study investigated 0.6 mg folic acid*
Cochrane, Kelsey M, Elango, Rajavel, Devlin, Angela M et al. (2023) Human milk unmetabolized folic acid is increased following supplementation with synthetic folic acid as compared to (6S)-5-methyltetrahydrofolic acid. Scientific reports 13(1): 11298	- Study conducted in general population and dose already established for this group *Study assessed 0.6 mg folic acid*
Cochrane, Kelsey M, Elango, Rajavel, Devlin, Angela M et al. (2023) Supplementation with (6S)-5-methyltetrahydrofolic acid appears as effective as folic acid in maintaining maternal folate status while reducing unmetabolised folic acid in maternal plasma: a randomised trial of pregnant women in Canada. The British journal of nutrition: 1-11	- Duplicate
Czeizel, Andrew E (2009) Periconceptional folic acid and multivitamin supplementation for the prevention of neural tube defects and other congenital abnormalities. Birth defects research. Part A, Clinical and molecular teratology 85(4): 260-8	- Study conducted in general population and dose already established for this group *Study investigated 0.8mg folic acid*
Czeizel, Andrew E. (2011) Periconceptional Folic Acid-Containing Multivitamin Supplementation for the Prevention of Neural	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion

Study	Code [Reason]
Tube Defects and Cardiovascular Malformations. Annals of Nutrition & Metabolism 59(1): 38-40	because studies do not compare different doses of folic acid.
Davis, Deborah J (1997) Periconceptional folic acid and the prevention of neural tube defects: Some food for thought for Canadian paediatricians. Paediatrics & child health 2(2): 114-119	- Ineligible study design *Questionnaire survey*
Dawson, D W (1966) Microdoses of folic acid in pregnancy. The Journal of obstetrics and gynaecology of the British Commonwealth 73(1): 44-8	- Ineligible study design *Prospective study*
Dawson, LE; Pham, B; Hunter, AGW (2001) Low rate of adequate folic acid supplementation in well-educated women of high socioeconomic status attending a genetics clinic. Canadian Medical Association Journal (CMAJ) 164(8): 1149-1150	- Ineligible study design *Research letter/comment*
De Ocampo, Maria P G, Araneta, Maria Rosario G, Macera, Caroline A et al. (2018) Folic acid supplement use and the risk of gestational hypertension and preeclampsia. Women and birth : journal of the Australian College of Midwives 31(2): e77-e83	- Ineligible intervention *Study does not compare two doses of folic acid*
De-Regil, Luz Maria, Fernandez-Gaxiola, Ana C, Dowswell, Therese et al. (2010) Effects and safety of periconceptional folate supplementation for preventing birth defects. The Cochrane database of systematic reviews: cd007950	- Duplicate
De-Regil, Luz Maria, Pena-Rosas, Juan Pablo, Fernandez-Gaxiola, Ana C et al. (2015) Effects and safety of periconceptional oral folate supplementation for preventing birth defects. The Cochrane database of systematic reviews: cd007950	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Desrosiers, T.A., Siega-Riz, A.M., Mosley, B.S. et al. (2018) Low carbohydrate diets may increase risk of neural tube defects. Birth Defects Research 110(11): 901-909	- Ineligible intervention *Study investigated association between carbohydrate intake and neural tube defects*
Dobo, M and Czeizel, A E (1998) Long-term somatic and mental development of children after periconceptional multivitamin	- Ineligible study outcomes *Study reported long term effects of multivitamin supplementation in childhood*

Study	Code [Reason]
supplementation. European journal of pediatrics 157(9): 719-23	
Dong, Jing, Yin, Lin-Liang, Deng, Xue-Dong et al. (2023) Initiation and duration of folic acid supplementation in preventing congenital malformations. BMC medicine 21(1): 292	- Ineligible study design *Prospective cohort study.*
Dwyer, Erin Rose, Filion, Kristian B, MacFarlane, Amanda J et al. (2022) Who should consume high-dose folic acid supplements before and during early pregnancy for the prevention of neural tube defects?. BMJ (Clinical research ed.) 377: e067728	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Edelstein, T, Stevens, K, Baumslag, N et al. (1968) Folic acid and vitamin B12 supplementation during pregnancy in a population subsisting on a sub-optimal diet. Journal of obstetrics and gynaecology of the British Commonwealth 75: 133-137	- Ineligible intervention *Study does not compare different doses of folic acid (both arms received 5mg folic acid)*
Einarson, A; Parshuram, C; Koren, G (2000) Periconceptional use of folic acid to reduce the rates of neural tube defects: is it working?. Reproductive toxicology (Elmsford, N.Y.) 14(4): 291-292	- Ineligible study design *Narrative commentary*
Fernandez-Roig, Silvia, Cavalle-Busquets, Pere, Fernandez-Ballart, Joan D et al. (2013) Low folate status enhances pregnancy changes in plasma betaine and dimethylglycine concentrations and the association between betaine and homocysteine. The American journal of clinical nutrition 97(6): 1252-9	- Ineligible study design *Prospective cohort study*
Fleming, A F, Martin, J D, Hahnel, R et al. (1974) Effects of iron and folic acid antenatal supplements on maternal haematology and fetal wellbeing. The Medical journal of Australia 2(12): 429-36	- Ineligible intervention *Study investigates the association between iron/folic acid on anaemia*
Furness, Denise, Fenech, Michael, Dekker, Gustaaf et al. (2013) Folate, vitamin B12, vitamin B6 and homocysteine: impact on pregnancy outcome. Maternal & child nutrition 9(2): 155-66	- Ineligible study design *Prospective cohort study*
Gao, Yunfei, Sheng, Chao, Xie, Ri-Hua et al. (2016) New Perspective on Impact of Folic Acid Supplementation during Pregnancy on Neurodevelopment/Autism in the Offspring	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.

Study	Code [Reason]
Children - A Systematic Review. PloS one 11(11): e0165626	
Gildestad, Trude, Bjorge, Tone, Haaland, Oystein A et al. (2020) Maternal use of folic acid and multivitamin supplements and infant risk of birth defects in Norway, 1999-2013. The British journal of nutrition 124(3): 316-329	- Ineligible study design *Prospective cohort study*
Gildestad, Trude, Bjorge, Tone, Vollset, Stein Emil et al. (2015) Folic acid supplements and risk for oral clefts in the newborn: a population-based study. The British journal of nutrition 114(9): 1456-63	- No information on folic acid dose available
Giles, P F; Harcourt, A G; Whiteside, M G (1971) The effect of prescribing folic acid during pregnancy on birth-weight and duration of pregnancy. A double-blind trial. The Medical journal of Australia 2(1): 17-21	- Study conducted in general population and dose already established for this group *Study investigated 5mg folic acid*
Giunta, G., Cardea, C., Matarazzo, M.G. et al. (2018) Is calcium levofolinate pentahydrate more effective than folic acid in young healthy women before conception?. Clinical and Experimental Obstetrics and Gynecology 45(5): 687-691	- Ineligible intervention *Study assesses whether levofolinic acid is better than folic acid to increase serum folate levels*
Gogou, Maria and Kolios, George (2020) Nutritional Supplements During Gestation and Autism Spectrum Disorder: What Do We Really Know and How Far Have We Gone?. Journal of the American College of Nutrition 39(3): 261-271	- Ineligible intervention *Study assesses impact of dietary supplements during pregnancy on the risk of autism spectrum disorder in the child*
Gomes, Filomena, Askari, Sufia, Black, Robert E et al. (2023) Antenatal multiple micronutrient supplements versus iron-folic acid supplements and birth outcomes: Analysis by gestational age assessment method. Maternal & child nutrition 19(3): e13509	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because none of the papers were from high income countries (as defined by the OECD).
Gunabalasingam, Sowmiya, De Almeida Lima Slizys, Daniele, Quotah, Ola et al. (2023) Micronutrient supplementation interventions in preconception and pregnant women at increased risk of developing pre-eclampsia: a systematic review and meta-analysis. European journal of clinical nutrition 77(7): 710-730	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search. *Relevant Wen 2018 paper included via primary sift.*
Guo, B.-Q., Li, H.-B., Zhai, D.-S. et al. (2019) Maternal multivitamin supplementation is associated with a reduced risk of autism	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion

Study	Code [Reason]
spectrum disorder in children: a systematic review and meta-analysis. Nutrition Research 65: 4-16	because studies do not compare different doses of folic acid.
Guo, Bao-Qiang, Li, Hong-Bin, Zhai, De-Sheng et al. (2019) Association of maternal prenatal folic acid intake with subsequent risk of autism spectrum disorder in children: A systematic review and meta-analysis. Progress in neuro-psychopharmacology & biological psychiatry 94: 109650	- Ineligible intervention *Study assesses association between folic acid and autism spectrum disorder*
Halicioglu, Oya, Sutcuoglu, Sumer, Koc, Feyza et al. (2012) Vitamin B12 and folate statuses are associated with diet in pregnant women, but not with anthropometric measurements in term newborns. The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians 25(9): 1618-21	- Ineligible study design *Cross-sectional study design*
Hampel, K and Roetz, R (1974) Influence of a long-time substitution with a folate-iron combination in pregnancy on serum folate and serum iron and on hematological parameters. Geburtshilfe und Frauenheilkunde 34: 409-417	- Not in English language
Hashemi, Mohammad, Heshmat-Ghahdarijani, Kiyan, Zarean, Elahe et al. (2016) Evaluation of the effect of high-dose folic acid on endothelial dysfunction in pre-eclamptic patients: A randomized clinical trial. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 21: 114	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Iran.*
Hodgetts, V A, Morris, R K, Francis, A et al. (2015) Effectiveness of folic acid supplementation in pregnancy on reducing the risk of small-for-gestational age neonates: a population study, systematic review and meta-analysis. BJOG : an international journal of obstetrics and gynaecology 122(4): 478-90	- Ineligible intervention *Study assesses timing of folic acid, not dose*
Holmes-Siedle, M., Dennis, J., Lindenbaum, R.H. et al. (1992) Long term effects of periconceptional multivitamin supplements for prevention of neural tube defects: A seven to 10 year follow up. Archives of Disease in Childhood 67(12): 1436-1441	- Ineligible study design *Prospective cohort study*

Study	Code [Reason]
Hossain, N, Kanani, FH, Ramzan, S et al. (2014) Obstetric and neonatal outcomes of maternal vitamin D supplementation: results of an open-label, randomized controlled trial of antenatal vitamin D supplementation in Pakistani women. Journal of clinical endocrinology and metabolism 99(7): 2448-2455	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Hunter, Patricia J, Muthiani, Yvonne, Nasanen-Gilmore, Pieta K et al. (2023) A modular systematic review of antenatal interventions to address undernutrition during pregnancy in the prevention of low birth weight. The American journal of clinical nutrition 117suppl2: 134-s147	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not compare different doses of folic acid.
Hursthouse, Nicola A, Gray, Andrew R, Miller, Jody C et al. (2011) Folate status of reproductive age women and neural tube defect risk: the effect of long-term folic acid supplementation at doses of 140 microg and 400 microg per day. Nutrients 3(1): 49-62	- Study conducted in general population and dose already established for this group *Study investigated 140mg and 400ug of folic acid*
Iglesias Vazquez, Lucia; Canals, Josefa; Arija, Victoria (2019) Review and meta-analysis found that prenatal folic acid was associated with a 58% reduction in autism but had no effect on mental and motor development. Acta paediatrica (Oslo, Norway : 1992) 108(4): 600-610	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.
Jarvenpaa, J, Schwab, U, Lappalainen, T et al. (2008) Mineral water fortified with folic acid and vitamins B6, B12, D and calcium improves folate status and decreases plasma homocysteine concentration in pregnant women. 35th nordic congress of obstetrics and gynecology; 2006 may 23-25; goteburg, sweden: 55	- Conference abstract
Kancherla, Vijaya, Botto, Lorenzo D, Rowe, Laura A et al. (2022) Preventing birth defects, saving lives, and promoting health equity: an urgent call to action for universal mandatory food fortification with folic acid. The Lancet. Global health 10(7): e1053-e1057	- Ineligible study design *Narrative summary*
Kannan, S, Menotti, E, Scherer, HK et al. (2007) Folic acid and the prevention of neural tube defects: a survey of awareness among Latina women of childbearing age residing in southeast Michigan. Health Promotion Practice 8(1): 60-68	- Ineligible study design *Survey*
Kelly, Dervla; O'Dowd, Tom; Reulbach, Udo (2012) Use of folic acid supplements and risk of	- Ineligible study design

Study	Code [Reason]
cleft lip and palate in infants: a population-based cohort study. The British journal of general practice : the journal of the Royal College of General Practitioners 62(600): e466-72	*Cross-sectional study design*
Kennedy, D; Pastuszak, A; Koren, G (1997) Taking folic acid during pregnancy. Don't leave it too late. Canadian family physician Medecin de famille canadien 43: 2113-4	- Ineligible study design *Information or leaflet for women in the pre-conception stage*
Kerr, Stephen M, Parker, Samantha E, Mitchell, Allen A et al. (2017) Periconceptional maternal fever, folic acid intake, and the risk for neural tube defects. Annals of epidemiology 27(12): 777-782e1	- Ineligible study design *Case-control study*
Kinnunen, Tarja I, Sletner, Line, Sommer, Christine et al. (2017) Ethnic differences in folic acid supplement use in a population-based cohort of pregnant women in Norway. BMC pregnancy and childbirth 17(1): 143	- No information on folic acid dose available
Kirke, P N; Daly, L E; Elwood, J H (1992) A randomised trial of low dose folic acid to prevent neural tube defects. The Irish Vitamin Study Group. Archives of disease in childhood 67(12): 1442-6	- Ineligible comparison *Compared low dose (0.36mg) folic acid supplement vs multivitamins with no folic acid.*
Koren, G (1993) Preconceptional folate and neural tube defects: time for rethinking. Canadian journal of public health = Revue canadienne de sante publique 84(3): 207-8	- Ineligible study design *Narrative commentary*
Lassi, Zohra S, Salam, Rehana A, Haider, Batool A et al. (2013) Folic acid supplementation during pregnancy for maternal health and pregnancy outcomes. The Cochrane database of systematic reviews: cd006896	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Laurence, K.M.; James, N.; Miller, M. (1982) A double randomised controlled trial for preconceptional folic acid supplementation for the prevention of recurrence of neural tube defects in high risk pregnancies. Journal of Medical Genetics 19(1): 66	- Conference abstract
Laurence, KM (1982) The role of maternal nutrition and folic acid therapy before conception to prevent neural tube defects. Monatsschrift fur Kinderheilkunde 130: 646	- Conference abstract

Study	Code [Reason]
Lira, P, Barrena, N, Foradori, A et al. (1989) Deficiency of folates in pregnancy: effect of supplementary folic acid. Sangre 34(1): 24-27	- Not in English language
Lira, P, Barrena, N, Foradori, A et al. (1989) Folate deficiency in pregnancy: effect of supplemental folate. Sangre 34: 24-27	- Not in English language
Liu, Cheng, Liu, Chongdong, Wang, Qiushi et al. (2018) Supplementation of folic acid in pregnancy and the risk of preeclampsia and gestational hypertension: a meta-analysis. Archives of gynecology and obstetrics 298(4): 697-704	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Meador, Kimford J, Pennell, Page B, May, Ryan C et al. (2020) Effects of periconceptional folate on cognition in children of women with epilepsy: NEAD study. Neurology 94(7): e729-e740	- Ineligible study design *Prospective cohort study*
Millar, Wayne J (2004) Folic acid supplementation. Health reports 15(3): 49-52	- No information on folic acid dose available
Mills, J L and Raymond, E (1993) Effects of recent research on recommendations for periconceptional folate supplement use. Annals of the New York Academy of Sciences 678: 137-45	- Ineligible study design *Cost-Benefit Analysis*
Monoarfa, Y, Gumilar, E, Widasari, L et al. (2020) The effect of selenium and multiple micronutrient administration during periconception period on the level of malondialdehyde. Enfermeria clinica 30suppl4: 114-118	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Indonesia.*
Morrow, J I, Hunt, S J, Russell, A J et al. (2009) Folic acid use and major congenital malformations in offspring of women with epilepsy: a prospective study from the UK Epilepsy and Pregnancy Register. Journal of neurology, neurosurgery, and psychiatry 80(5): 506-11	- Ineligible intervention *Unclear what dose of folic acid was given to women in intervention group (some had high dose of 5mg and some had 400mcg)*
Muchowski, Karen and Paladine, Heather (2004) An ounce of prevention: the evidence supporting periconception health care. The Journal of family practice 53(2): 126-33	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.

Study	Code [Reason]
Murphy, Malia S Q, Muldoon, Katherine A, Sheyholislami, Hauna et al. (2021) Impact of high-dose folic acid supplementation in pregnancy on biomarkers of folate status and 1-carbon metabolism: An ancillary study of the Folic Acid Clinical Trial (FACT). The American journal of clinical nutrition 113(5): 1361-1371	- Ineligible intervention *Study assesses folate and 1-carbon metabolism biomarkers in pregnant women*
Murphy, P A (1992) Periconceptional supplementation with folic acid. Does it prevent neural tube defects?. Journal of nurse-midwifery 37(1): 25-32	- Ineligible study design *Literature review*
Nilsen, Roy M, Vollset, Stein E, Gjessing, Hakon K et al. (2006) Patterns and predictors of folic acid supplement use among pregnant women: the Norwegian Mother and Child Cohort Study. The American journal of clinical nutrition 84(5): 1134-41	- Ineligible study design *Prospective cohort study*
Nkrumah, Isaac, North, Madelon, Kothe, Emily et al. (2020) The Relationship Between Pregnancy Intentions and Diet or Physical Activity Behaviors in the Preconception and Antenatal Periods: A Systematic Review and Meta-Analysis. Journal of midwifery & women's health 65(5): 660-680	- Ineligible intervention *Study assesses the association between women's pregnancy intentions and diet or physical activity behaviours in the preconception and antenatal periods*
O'Malley, Eimer G, Reynolds, Ciara M E, Cawley, Shona et al. (2018) Folate and vitamin B12 levels in early pregnancy and maternal obesity. European journal of obstetrics, gynecology, and reproductive biology 231: 80-84	- Ineligible population *Study based on women with a BMI ≥25kg/m^2*
Obeid, Rima, Schon, Christiane, Wilhelm, Manfred et al. (2018) The effectiveness of daily supplementation with 400 or 800 microg/day folate in reaching protective red blood folate concentrations in non-pregnant women: a randomized trial. European journal of nutrition 57(5): 1771-1780	- Study conducted in general population and dose already established for this group *Study investigated 400ug or 800ug folic acid*
Oulhote, Youssef, Lanphear, Bruce, Braun, Joseph M. et al. (2020) Gestational Exposures to Phthalates and Folic Acid, and Autistic Traits in Canadian Children. Environmental Health Perspectives 128(2): 027004-1	- Ineligible intervention *Study assesses the relationship between gestational phthalates and autistic traits in 3 to 4 year old children*
Ozerol, Elif, Ozerol, Ibrahim, Gokdeniz, Remzi et al. (2004) Effect of smoking on serum concentrations of total homocysteine, folate,	- Ineligible intervention

Study	Code [Reason]
vitamin B12, and nitric oxide in pregnancy: a preliminary study. Fetal diagnosis and therapy 19(2): 145-8	*Study assesses differences in the serum levels between smoking and non-smoking pregnant women*
Park, Hyesook, Kim, Young Ju, Ha, Eun Hee et al. (2004) The risk of folate and vitamin B(12) deficiencies associated with hyperhomocysteinemia among pregnant women. American journal of perinatology 21(8): 469-75	- Ineligible intervention *Study compares folate and vitamin B12 levels in pregnant and nonpregnant women to evaluate the risk for hyperhomocysteinemia and for folate and vitamin B12 deficiencies during pregnancy*
Partap, Uttara, Chowdhury, Ranadip, Taneja, Sunita et al. (2022) Preconception and periconception interventions to prevent low birth weight, small for gestational age and preterm birth: a systematic review and meta-analysis. BMJ global health 7(8)	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.
Pereira, Abilio and Keating, Elisa (2023) Maternal folate and metabolic programming of the offspring: A systematic review of the literature. Reproductive toxicology (Elmsford, N.Y.) 120: 108439	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Pritchard, J A; Scott, D E; Whalley, P J (1971) Maternal folate deficiency and pregnancy wastage. IV. Effects of folic acid supplements, anticonvulsants, and oral contraceptives. American journal of obstetrics and gynecology 109(3): 341-6	- Ineligible intervention *Study assesses the role of folate supplements, pregnancy and oral contraceptives in megaloblastic anaemia*
Ramakrishnan, Usha, Grant, Frederick Kobina, Goldenberg, Tamar et al. (2012) Effect of multiple micronutrient supplementation on pregnancy and infant outcomes: a systematic review. Paediatric and perinatal epidemiology 26suppl1: 153-67	- Ineligible intervention *Systematic review does not compare different doses of folic acid*
Ramakrishnan, Usha, Grant, Frederick Kobina, Imdad, Aamer et al. (2013) Effect of multiple micronutrient versus iron-folate supplementation during pregnancy on intrauterine growth. Nestle Nutrition Institute workshop series 74: 53-62	- No information on folic acid dose available
Ray, Joel G and Mamdani, Muhammad M (2002) Association between folic acid food fortification and hypertension or preeclampsia in pregnancy. Archives of internal medicine 162(15): 1776-7	- Ineligible study design *Retrospective longitudinal study*

Study	Code [Reason]
Ray, Joel G, Wyatt, Philip R, Vermeulen, Marian J et al. (2005) Greater maternal weight and the ongoing risk of neural tube defects after folic acid flour fortification. Obstetrics and gynecology 105(2): 261-5	- Ineligible study design *Retrospective cohort study*
Renard, Emeline, Leheup, Bruno, Gueant-Rodriguez, Rosa-Maria et al. (2020) Folinic acid improves the score of Autism in the EFFET placebo-controlled randomized trial. Biochimie 173: 57-61	- Ineligible population *Study included children with autistic spectrum disorder*
Rhoads, G G and Mills, J L (1986) Can vitamin supplements prevent neural tube defects? Current evidence and ongoing investigations. Clinical obstetrics and gynecology 29(3): 569-79	- Ineligible study design *Literature review*
Riaz, Musarrat, Shaikh, Fareeha, Fawwad, Asher et al. (2018) Maternal Nutrition during Early Pregnancy and Cardiometabolic Status of Neonates at Birth. Journal of diabetes research 2018: 7382946	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Rolschau, J; Date, J; Kristoffersen, K (1979) Folic acid supplement and intrauterine growth. Acta obstetricia et gynecologica Scandinavica 58(4): 343-6	- Ineligible study design *Prospective cohort study*
Rose, Elaine G, Murphy, Malia S Q, Erwin, Erica et al. (2021) Gestational Folate and Folic Acid Intake among Women in Canada at Higher Risk of Pre-Eclampsia. The Journal of nutrition 151(7): 1976-1982	- Ineligible study design *Secondary analysis of randomised controlled trial*
Rucklidge, Julia J, Eggleston, Matthew J F, Darling, Kathryn A et al. (2019) Can we predict treatment response in children with ADHD to a vitamin-mineral supplement? An investigation into pre-treatment nutrient serum levels, MTHFR status, clinical correlates and demographic variables. Progress in neuro-psychopharmacology & biological psychiatry 89: 181-192	- Ineligible population *Study investigated children with ADHD*
Saccone, Gabriele and Berghella, Vincenzo (2016) Folic acid supplementation in pregnancy to prevent preterm birth: a systematic review and meta-analysis of randomized controlled trials. European journal of obstetrics, gynecology, and reproductive biology 199: 76-81	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.

Study	Code [Reason]
Sadeeqa, S., Aslam, F., Zafar, M. et al. (2019) Relationship of medications and pregnancy complications. Journal of Medical Sciences (Peshawar) 27(3): 213-219	- Ineligible study design *Cross-sectional study design*
Sayyah-Melli, Manizheh, Ghorbanihaghjo, Amir, Alizadeh, Mahasti et al. (2016) The Effect of High Dose Folic Acid throughout Pregnancy on Homocysteine (Hcy) Concentration and Pre-Eclampsia: A Randomized Clinical Trial. PloS one 11(5): e0154400	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Iran.*
Shaw, M T and Hoffbrand, A V (1970) The use and abuse of folic acid. The Practitioner 204(224): 795-804	- Ineligible study design *Literature review*
Shere, Mahvash, Nguyen, Patricia, Tam, Carolyn et al. (2015) Pregnancy-induced changes in the long-term pharmacokinetics of 1.1 mg vs. 5 mg folic acid: a randomized clinical trial. Journal of clinical pharmacology 55(2): 159-67	- Study data presented graphically and cannot be used in analysis
Shim, Sang-Min; Yun, Yeo-Ul; Kim, Yun Sook (2016) Folic acid alone or multivitamin containing folic acid intake during pregnancy and the risk of gestational hypertension and preeclampsia through meta-analyses. Obstetrics & gynecology science 59(2): 110-5	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Shiralizadeh, Javad, Barmaki, Haleh, Haiaty, Sanya et al. (2017) The effects of high and low doses of folic acid on oxidation of protein levels during pregnancy: a randomized double-blind clinical trial. Hormone molecular biology and clinical investigation 33(3)	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Dubai.*
Siddiqui, M.; Khatri, I.A.; Ahmad, A. (2014) Maternal and fetal complications in pregnant epileptic women. Rawal Medical Journal 39(2): 174-177	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in Pakistan.*
Stern, S.J., Matok, I., Kapur, B. et al. (2011) A comparison of folic acid pharmacokinetics in obese and nonobese women of childbearing age. Therapeutic Drug Monitoring 33(3): 336-340	- Ineligible population *Study population is women with a BMI ≥25kg/m^2*
Suzuki, T., Nishigori, T., Obara, T. et al. (2022) Maternal folic acid supplement use/dietary folate	- Ineligible study design

Study	Code [Reason]
intake from preconception to early pregnancy and neurodevelopment in 2-year-old offspring: the Japan Environment and Children's Study. British Journal of Nutrition 128(12): 2480-2489	*Prospective cohort study.*
Takacs, P and Rodriguez, L (2005) High folic acid levels and failure of single-dose methotrexate treatment in ectopic pregnancy. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 89(3): 301-2	- Conference abstract
Tamura, Tsunenobu, Goldenberg, Robert L, Chapman, Victoria R et al. (2005) Folate status of mothers during pregnancy and mental and psychomotor development of their children at five years of age. Pediatrics 116(3): 703-8	- Ineligible study design *Retrospective cohort study*
Tchernia, G, Blot, I, Rey, A et al. (1982) Maternal folate status, birthweight and gestational age. Developmental Pharmacology Therapeutics 4: 58-65	- Article unavailable
Ter Borg, Sovianne; Koopman, Nynke; Verkaik-Kloosterman, Janneke (2023) An Evaluation of Food and Nutrient Intake among Pregnant Women in The Netherlands: A Systematic Review. Nutrients 15(13)	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion or have already been included through main search.
Trigg, K H, Rendall, E J, Johnson, A et al. (1976) Folate supplements during pregnancy. The Journal of the Royal College of General Practitioners 26(164): 228-30	- Ineligible intervention *Study does not compare different doses of folic acid. Study compares two doses of ferrous sulphate*
Tuenter, Annelies, Bautista Nino, Paula K, Vitezova, Anna et al. (2019) Folate, vitamin B12, and homocysteine in smoking-exposed pregnant women: A systematic review. Maternal & child nutrition 15(1): e12675	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not compare different doses of folic acid.
Turck, Dominique, Bohn, Torsten, Castenmiller, Jacqueline et al. (2023) Scientific opinion on the tolerable upper intake level for folate. EFSA journal. European Food Safety Authority 21(11): e08353	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.
Ulrich, Cornelia M and Potter, John D (2006) Folate supplementation: too much of a good thing?. Cancer epidemiology, biomarkers & prevention : a publication of the American	- Ineligible study design *Narrative commentary*

Study	Code [Reason]
Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 15(2): 189-93	
Ulrich, M, Kristoffersen, K, Rolschau, J et al. (1999) The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part II. Congenital anomalies. A randomised study. European journal of obstetrics, gynecology, and reproductive biology 87(2): 111-4	- Unclear how many participants randomised to each arm
Ulrich, M, Kristoffersen, K, Rolschau, J et al. (1999) The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. Part III. Congenital anomalies. An observational study. European journal of obstetrics, gynecology, and reproductive biology 87(2): 115-4	- Ineligible study design *Retrospective cohort study*
US Preventive Services Task, Force, Bibbins-Domingo, Kirsten, Grossman, David C et al. (2017) Folic Acid Supplementation for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. JAMA 317(2): 183-189	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.
van der Windt, Melissa, van der Kleij, Rianne Maria, Snoek, Katinka Marianne et al. (2020) Impact of a Blended Periconception Lifestyle Care Approach on Lifestyle Behaviors: Before-and-After Study. Journal of medical Internet research 22(9): e19378	- Ineligible intervention *Study assesses the effectiveness of a periconceptional lifestyle intervention on the improvement of lifestyle components*
Van Dyke, Don C, Stumbo, Phyllis J, Mary, J Berg et al. (2002) Folic acid and prevention of birth defects. Developmental Medicine & Child Neurology 44(6): 426-429	- Ineligible study design *Literature review*
van Gellekom, S.A., Lindauer-van der Werf, G., Hague, W.M. et al. (2008) Anaemia and haemolysis in pregnancy due to rapid folic acid and vitamin B12 depletion. Netherlands Journal of Medicine 66(5): 216-217	- Ineligible study design *Case report*
Virk, Jasveer, Liew, Zeyan, Olsen, Jorn et al. (2016) Preconceptional and prenatal supplementary folic acid and multivitamin intake and autism spectrum disorders. Autism : the international journal of research and practice 20(6): 710-8	- Ineligible study outcomes *Study reported on autism spectrum disorders in children*

Study	Code [Reason]
Virk, Jasveer, Liew, Zeyan, Olsen, Jorn et al. (2018) Pre-conceptual and prenatal supplementary folic acid and multivitamin intake, behavioral problems, and hyperkinetic disorders: A study based on the Danish National Birth Cohort (DNBC). Nutritional neuroscience 21(5): 352-360	- Ineligible study design *Prospective cohort study*
Viswanathan, M, Urrutia, RP, Hudson, KN et al. (2023) Folic Acid Supplementation to Prevent Neural Tube Defects: A Limited Systematic Review Update for the U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Evidence Syntheses, formerly Systematic Evidence Reviews	- Duplicate
Viswanathan, Meera, Urrutia, Rachel Peragallo, Hudson, Kesha N et al. (2023) Folic Acid Supplementation to Prevent Neural Tube Defects: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 330(5): 460-466	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes. *1 RCT was included in this SR (Bortolus 2021), which was screened out via primary sift.*
Wald, N (1993) Folic acid and the prevention of neural tube defects. Annals of the New York Academy of Sciences 678: 112-29	- Ineligible study design *Narrative comment/letter*
Wald, N J and Bower, C (1994) Folic acid, pernicious anaemia, and prevention of neural tube defects. Lancet (London, England) 343(8893): 307	- Conference abstract
Wald, N J, Hackshaw, A, Stone, R et al. (1993) Serum alpha-fetoprotein and neural tube defects in the first trimester of pregnancy. MRC Vitamin Study Research Group. Prenatal diagnosis 13(11): 1047-50	- No information on folic acid dose available
Wald, N.J. (2004) Folic Acid and the Prevention of Neural-Tube Defects. New England Journal of Medicine 350(2): 101-103	- Ineligible study design *Case-control study*
Wen, S W, Champagne, J, Rennicks White, R et al. (2012) OS040. Effect of folic acid supplementation in pregnancy on preeclampsia-Folic acid clinical trial (FACT). Pregnancy hypertension 2(3): 198	- Trial protocol
Wen, S.W., White, R.R., Rybak, N. et al. (2019) Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (fact): Double	- Duplicate

Study	Code [Reason]
blind, Phase III, randomised controlled, international, multicentre trial. Obstetrical and Gynecological Survey 74(2): 68-70	
Wen, Shi Wu, Guo, Yanfang, Rodger, Marc et al. (2016) Folic Acid Supplementation in Pregnancy and the Risk of Pre-Eclampsia-A Cohort Study. PloS one 11(2): e0149818	- Ineligible study design *Prospective cohort study*
Wen, SW, White, RR, Rybak, N et al. (2019) Effect of high dose folic acid supplementation in pregnancy on pre-eclampsia (fact): double blind, Phase III, randomised controlled, international, multicentre trial. Obstetrical & gynecological survey 74(2): 68-70	- Duplicate
Willoughby, M L and Jewell, F G (1968) Folate status throughout pregnancy and in postpartum period. British medical journal 4(5627): 356-60	- Ineligible study design *Prospective cohort study*
Willoughby, M L and Jewell, F J (1966) Investigation of folic acid requirements in pregnancy. British medical journal 2(5529): 1568-71	- Ineligible study outcomes *Study reports on incidence of megaloblastic anaemia of pregnancy*
Wilson, R Douglas and O'Connor, Deborah L (2022) Guideline No. 427: Folic Acid and Multivitamin Supplementation for Prevention of Folic Acid-Sensitive Congenital Anomalies. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 44(6): 707-719e1	- Ineligible study design *Guideline recommendations*
Withanage, Nishadi N, Botfield, Jessica R, Srinivasan, Sonia et al. (2022) Effectiveness of preconception interventions in primary care: a systematic review. The British journal of general practice : the journal of the Royal College of General Practitioners 72(725): e865-e872	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not have eligible outcomes.
Yang, Yan; Cai, Zixin; Zhang, Jingjing (2021) Association between maternal folate status and gestational diabetes mellitus. Food science & nutrition 9(4): 2042-2052	- Ineligible study design *Study reports on gestational diabetes mellitus*
Yang, Yan; Cai, Zixin; Zhang, Jingjing (2021) The effect of prepregnancy body mass index on maternal micronutrient status: a meta-analysis. Scientific reports 11(1): 18100	- Ineligible intervention *Study assesses the effect between prepregnancy body mass index and maternal micronutrient status*

Study	Code [Reason]
Yerby, Mark S (2003) Clinical care of pregnant women with epilepsy: neural tube defects and folic acid supplementation. Epilepsia 44suppl3: 33-40	- Ineligible study design *Literature review*
Yi, Yunni, Lindemann, Marion, Colligs, Antje et al. (2011) Economic burden of neural tube defects and impact of prevention with folic acid: a literature review. European journal of pediatrics 170(11): 1391-400	- Ineligible study design *Literature review*
Yusuf, Korede K, Salihu, Hamisu M, Wilson, Ronee et al. (2019) Folic Acid Intake, Fetal Brain Growth, and Maternal Smoking in Pregnancy: A Randomized Controlled Trial. Current developments in nutrition 3(6): nzz025	- Ineligible study outcomes *Study reports on prenatal fetal brain growth, measured by head circumference, brain weight, and brain-body weight ratio*
Zheng, Lili, Huang, Jing, Kong, Hongfang et al. (2020) The effect of folic acid throughout pregnancy among pregnant women at high risk of pre-eclampsia: A randomized clinical trial. Pregnancy hypertension 19: 253-258	- Ineligible country *Not high-income country (as defined by the OECD) as specified in the protocol. Study was conducted in China.*
Zhong, Caichen, Tessing, Jillian, Lee, Brian K et al. (2020) Maternal Dietary Factors and the Risk of Autism Spectrum Disorders: A Systematic Review of Existing Evidence. Autism research : official journal of the International Society for Autism Research 13(10): 1634-1658	- Systematic review. Included studies checked for eligibility. No studies identified for inclusion because studies do not compare different doses of folic acid.
Zia, S., Rafique, M., Khan, M.A. et al. (2015) Demographic and clinical characteristics of children with sickle cell disease. Pakistan Paediatric Journal 39(2): 85-92	- Ineligible study design *Cross-sectional study*

Excluded economic studies

No economic study was reviewed at full text and excluded from this review.

Appendix K Research recommendations – full details

Research recommendations for review question: Which groups of women should be advised to take high-dose folic acid supplements before and during the first 12 weeks of pregnancy?

Research recommendation

What is the most effective and safe dose for folic acid supplementation before and during the first 12 weeks of pregnancy for people at a high risk of conceiving a child with a neural tube defect?

Why this is important

There was no evidence to support the use of the high-dose (5 mg) folic acid during preconception and pregnancy for people at greater risk of delivering a baby with a neural tube defect. Research in this topic will add additional clarity to what is the optimal supplemental dose of folate to help prevent neural tube defects in high-risk pregnancies.

Rationale for research recommendation

Table 10: Research recommendation rationale

Importance to 'patients' or the population	Currently there is no evidence to support the use of the 5 mg higher supplemental dose of folate recommended for people at greater risk of delivering a baby with a neural tube defect. Most other middle to high income countries recommend a supplement of between 1-4 mg for high-risk pregnancies. It is important to determine whether we are currently over-supplementing, and this is even more relevant given the imminent mandatory fortification of flour with folate.
Relevance to NICE guidance	NICE currently recommends high dose (5 mg folic acid /day) when planning a pregnancy or in early stages of pregnancy for personal or partner history of neural tube defect (NTD), previous baby with NTD, personal or partner family history of NTDs, type 1 or type 2 diabetes, and when taking an antiepileptic drug. For low risk people, a dose of 400 micrograms/day is recommended for all people planning pregnancy or who are pregnant (PH11, CG137). NICE currently does not recommend high dose folic acid for pregnant people with obesity. This proposed research will add additional clarity to what is the optimal supplemental dose of folate to help prevent neural tube defects in high-risk pregnancies.
Relevance to the NHS	There is no high-quality evidence that periconceptional high dose folic acid is associated with adverse outcomes but possible adverse effects cannot be excluded. In addition to NICE recommendations, the Royal College of Obstetricians recommends that people with obesity take high dose (5 mg) of folic acid daily, based on greater risk of neural tube defects and lower folate status, but without supporting evidence from observational studies or trials.
National priorities	High
Current evidence base	No evidence was identified on high-dose (5 mg) folic acid during preconception and pregnancy, although 5 mg is the current recommended dose for those with an increased risk of conceiving a child with neural tube defects or other congenital malformations, so the committee made a research recommendation.
Equality considerations	Ethnicity and socio-economic factors

mg: milligrams; NICE: National Institute for Health and Care Excellence; NHS: National Health Service; NTD: neural tube defect

Modified PICO table

Table 11: Research recommendation modified PICO table

Population	People at risk of neural tube defect (NTDs) who are trying to become pregnant or people during the first 12 weeks of a single or multiple pregnancy.
Intervention	High-dose folic acid supplementation (5 mg daily with no additional vitamins/minerals) provided ≥12 weeks prior to conception and for at least the first trimester.
Comparator	• Low-dose folic acid supplementation (<1 mg daily with no additional vitamins/minerals) provided ≥12 weeks prior to conception and for at least the first trimester. • Medium-dose folic acid supplementation (≥1 to <5 mg daily with no additional vitamins/minerals) provided ≥12 weeks prior to conception and for at least the first trimester.
Outcome	Primary outcomes • Neural tube defects (NTDs) in the baby • Birthweight centile • Compliance Secondary outcomes • Congenital heart defects • Midline facial defects such as cleft lip or cleft palate • Red blood cell (RBC) (or serum if RBC is not reported) folate concentrations in the mother • Infant neurocognitive outcomes e.g. ASQ • Childhood neurodevelopmental outcomes (dichotomous outcome, not continuous outcomes such as mean change in score): - Severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of mental development index [MDI] or psychomotor developmental index [PDI]) -Moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84) • Cost-effectiveness (including resource use measurements and QALY estimations using a validated preference-based measure such as the EQ-5D or SF-6D)
Study design	RCTs
Timeframe	Short- term follow-up (for diagnosis of congenital malformation during pregnancy or at delivery) and medium-term follow-up (for neurodevelopment outcomes which is 2- 5 years post-delivery)
Additional information	Sub-group analysis: 1. Single versus multiple pregnancies 2. Women with a previous history of a pregnancy affected by a neural tube defect versus not 3. Women with diabetes (type 1 and type 2) versus not 4. Socio economic status and deprivation (measured using IMD) 5. BMI ≤ 25 kg/m^2 versus BMI ≥ 25 kg/m^2 or more 6. Age <40 years versus ≥40 years 7. Ethnicity 8. Women who smoke versus not

ASQ: The Ages and Stages Questionnaire; EQ-5D: European Quality of Life Five Dimension; MDI: mental development index; mg: milligrams; NTDs: neural tube defects; PDI: psychomotor developmental index; RCT: randomized controlled trials; SF-6D: Short-Form Six-Dimension; SD: standard deviation; QALY: The quality-adjusted life-year