National Institute for Health and Care Excellence

Draft for consultation

Maternal and child nutrition

[C] Evidence reviews interventions to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy

NICE guideline number tbc

Evidence reviews underpinning recommendations 1.1.1 to 1.1.3 and 1.1.8 in the NICE guideline

June 2024

Draft for consultation

This 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 All NICE guidance is subject to regular review and may be updated or withdrawn.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:

Contents

Interventions to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy

Review question

What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Introduction

To reduce the risk of neural tube defects (NTDs), current UK guidance recommends that those who could become pregnant should take a daily 400 micrograms folic acid supplement before conception and until the 12th week of pregnancy. Some groups with increased risk of NTDs) are recommended to take a higher dose. However, it is recognised that compliance with these guidelines is poor with one UK study suggesting that only 31% of women reported taking folic acid supplements as recommended in their most recent pregnancy (Barbour 2012). Another cross-sectional survey of women attending three maternity centres across London investigating knowledge and uptake of preconception care found that 51% of all the women took folic acid before their pregnancy (Stephenson 2014).

It is important to explore how the uptake of folic acid supplements can be improved in both the preconception period and during the first 12 weeks of pregnancy. The aim of this evidence review is to determine which interventions are effective in increasing uptake of folic acid supplementation 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 planning to become pregnant • Pregnant women during the first 12 weeks of a single or multiple pregnancy
Intervention	• **Intervention group 1:** Interventions using information provision and/or education • **Intervention group 2:** Interventions using alternative forms of folic acid supplementation (drops or tablets) • **Intervention group 3:** Interventions aimed at improving access to folic acid supplementation (that is, provision of folic acid supplementation in different settings or incorporation of folic acid in welfare schemes) • **Intervention group 4:** Interventions using psychological or behavioural techniques • **Intervention group 5:** Multicomponent interventions (interventions that combine more than 1 intervention listed above) The committee anticipated that, along with the intervention, studies would report at least 1 component of each of the groups noted below. Sensitivity analyses will be done according to these if enough data is available. • **Component 1:** Mode of delivery • **Component 2:** When is the intervention delivered • **Component 3:** Intervention aimed at individuals or groups • **Component 4:** Individualised or tailored interventions • **Component 5:** Who delivers the intervention • **Component 6:** Where is the intervention delivered • **Component 7**: Behaviour change models, techniques and theories
Comparison	• One of the above interventions (within the same group or different group interventions will be considered) • Status quo/treatment as usual (as defined by study authors, includes no treatment) • Time (before and after)

Outcome	**Critical**
	• Changes in folic acid supplementation uptake rate (self-reported or objective measures)
	
	Important
	• Changes in attitude, confidence, and knowledge as part of people's intention to change behaviour
	• Unintended consequences:
	  ○ Increase in inequalities
	  ○ Supplementation wastage

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

Fifteen studies were included for this review, 2 randomised controlled trials (Schwarz 2008 and Van Dijk 2020), 2 cluster randomised controlled trials (Geyer 2022 and Chilukuri 2018), 1 prospective cohort study (Watkins 2004), 1 retrospective cohort study (Tripathi 2010), 1 controlled before-and-after study (Van Dijk 2016) and 8 uncontrolled before-and-after studies (Anwar 2011, de Weerd 2002, deRosset 2014, Flores 2017, Holmes 2017, Morgan 2009, Murphy 2010, Yamamoto 2018).

The included studies are summarised in Table 2.

Included studies reported the following comparisons:

- Six studies compared folic acid information/education provision to status quo treatment including no treatment (Anwar 2011, Holmes 2017, Murphy 2010, Tripathi 2010, Van Dijk 2016 and Yamamoto 2018).
- Two studies compared folic acid tailored information/education provision to other forms of information/education provision (defined as general brief information and limited information without personalisation respectively; Geyer 2022 and Van Dijk 2020).
- Four studies compared multicomponent interventions of folic acid information/education provision and folic acid supply to before intervention (de Weerd 2002, deRosset 2014, Flores 2017 and Morgan 2009).
- One study compared multicomponent interventions of folic acid information/education provision to another multicomponent intervention of general information/education provision and folic acid supply (Chilukuri 2018).
- One study compared multicomponent intervention of folic acid information/education provision and folic acid supply to another multicomponent intervention of emergency contraception information/education provision and emergency contraception supply (Schwarz 2008).
- One study compared multicomponent intervention of folic acid information/education provision and folic acid supply to folic acid information/education provision only (Watkins 2004).

Interventions using alternative forms of folic acid supplementation (drops or tablets) and interventions aimed at improving access to folic acid supplementation (that is, provision of folic acid supplementation in different settings or incorporation of folic acid in welfare schemes) were only reported in combination with other interventions.

Thirteen studies reported on the critical outcome changes in folic acid supplementation uptake (Anwar 2011, Chilukuri 2018, de Weerd 2002, Flores 2017, Geyer 2022, Holmes 2017, Morgan 2009, Murphy 2010, Tripathi 2010, Van Dijk 2016, Van Dijk 2020, Watkins 2004, and Yamamoto 2018), 4 studies reported on the important outcome changes in knowledge as part of people's intention to change behaviour (deRosset 2014, Flores 2017, Schwarz 2008 and Watkins 2004).

No evidence was found that reported on the important outcomes changes in attitude and confidence, and unintended consequences of the interventions such as increase in inequalities or supplementation wastage.

Studies were analysed separately by study design and estimates reported. For example, randomised controlled trials were not pooled with cohort studies and controlled/uncontrolled before-and-after studies.

Sensitivity analysis on the following component domains along with the interventions were planned if there was enough data available: component 1 mode of delivery, component 2

when the intervention is delivered, component 3 intervention aimed at individuals or groups, component 4 individualised/tailored interventions or general, component 5 who delivers the intervention, component 6 where the intervention is delivered, component 7 behaviour change models, techniques and theories. Sensitivity analysis for the various components of interventions was conducted for outcomes with at least 2 studies.

As per protocol, the evidence was stratified by BMI thresholds and comorbidities (women with pregestational diabetes). This included a subgroup of women with pregestational diabetes who took 5 mg of folic acid dosage daily, which was reported in subgroup analysis. There was insufficient evidence to conduct analysis for other strata specified in the protocol (folic acid supplementation dosage, age, and deprived socioeconomic background). It was not possible to conduct subgroup analysis as there was no heterogeneity in the evidence.

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
Anwar 2011 Uncontrolled before-and-after study United Kingdom	N=57 Women with diabetes who attended a pre-pregnancy care clinic and subsequently achieved pregnancy in 1997-2007 Mean age in years (SD): Not reported Mean age in years (range): 28.5 (19-40) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported Mean parity (range) 0.7 (0-4)	Pre-pregnancy counselling Review and consideration of medical conditions, drug treatment, smoking and alcohol use, obstetrics and gynaecological history and advice on glycaemic control to optimise HbA1c levels and organise screening for diabetic complications. No further information on folic acid advice reported in the paper.	Data recorded at the booking visit when pregnancy was achieved.	• Folic acid supplementation uptake at 8 weeks	Study did not adjust for confounders

Study	Population	Intervention	Comparison	Outcomes	Comments
	Mean duration of diabetes (SD), years: 10.9 (NR, range 0.1 - 37)				
Chilukuri 2018 Cluster randomised controlled trial USA	N = 415 Biologic mothers presenting with a child <12 months for paediatric care Mean age of mother in years (SD): Intervention group: 26.5 (6.2) Control group: 26.4 (6.0) Mean BMI in kg/m^2 (SD): not reported Parity (n, %): Not reported Mean previous live birth (SD): Intervention group: 2.08 (1.25) Control group: 1.95 (1.21)	<u>Focused counselling (including folic acid supply) ahead of a subsequent pregnancy</u> Receipt of Centers for Disease Control and Prevention (CDC) preconception women's health handout, a 90-day supply of multivitamins containing 400 micrograms folate, completing of a preconception health screener to assess risk factors including folate intake and tailored counselling	<u>No focused counselling (including folic acid supply)</u> Receipt of CDC preconception women's health handout and a 90-day supply of multivitamins containing 400 micrograms folate	• Folic acid supplementation uptake at 6 months after intervention	Study adjusted for age of mother, age of child, race/ethnicity, education, income, parity, and intention to have a pregnancy in the next 6 months.
de Weerd 2002 Uncontrolled before-and-after study The Netherlands	N = 111 Couples with a scheduled appointment at a fertility clinic or at clinic for preconception care Mean age in years (SD): Not reported Age (n, %) in years	<u>Counselling</u> Counselling about relevant aspects of health promotion including smoking cessation, nutritional habits, antenatal care and folic acid supplement intake	<u>Before counselling</u>	• Folic acid supplementation uptake (measured as serum folate) at 4 months	Study did not adjust for confounders

Study	Population	Intervention	Comparison	Outcomes	Comments
	25-29: 23 (20.7) 30–34: 55 (49.5) 35–39:31 (27.9) ≥40: 2 (1.8) Mean BMI in kg/m^2 (SD): not reported Parity (n, %): Not reported Obstetric history, (n, %): Never pregnant: 66 (59.5) Prior birth: 36 (32.4),				
de Rosset 2014 Uncontrolled before-and-after study USA	N = 303 Non pregnant females able to have children Mean age in years (SD): Not reported, Participants who completed study: 30 (7.6) Participants lost to follow-up: 31(6.6) Age range in years: 18-45 Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Participants who completed study Parous: not reported (87)	<u>Educational intervention workshop (including folic acid supply)</u> Education information about folic acid, vitamins and the prevention of NTDs, educational brochures and 90-day supply of multivitamins containing 400 micrograms folic acid	<u>Before intervention</u>	• Change in knowledge at 4 months	Study did not adjust for confounders

Study	Population	Intervention	Comparison	Outcomes	Comments
	Nuliparous: not reported (13) Participants lost to follow-up Parous: not reported (84 Nuliparous: not reported (16)				
Flores 2017 Uncontrolled before-and-after study USA	N = 1756 Hispanic women Mean age in years (SD): 33 (NR) Age range in years: 18-45 Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Nulliparous: 172 (12) Parous: 172 (12)	<u>Educational session (including folic acid supply)</u> 1 to 2 hours educational session about folic acid and neural tube defects and a 90-day supply of multivitamins containing folic acid	<u>Before intervention</u>	• Folic acid supplementation uptake at 4 months • Change in knowledge at 4 months	Study did not adjust for confounders
Geyer 2022 Cluster randomised controlled trial Germany	N = 10 clusters, 2099 participants Pregnant women <12 weeks gestation Mean pre-pregnancy age in years (SD): Intervention group: 30.1 (4.3) Control group: 30.3 (4.6) Mean BMI in kg/m^2 (SD): Not reported	<u>Lifestyle counselling</u> Topics of healthy diet and dietary supplementation during pregnancy (including information on the increased need for vitamins and mineral nutrients as well as the importance of iodine and folic acid micronutrients), physical activity and appropriate weight gain, all based on	<u>Routine medical examinations</u> Routine examinations during pregnancy along with a flyer and brochures with brief and general information on healthy lifestyle during pregnancy	• Folic acid supplementation uptake in first trimester of pregnancy	Study adjusted for pre-pregnancy BMI category, age, educational level and parity

Study	Population	Intervention	Comparison	Outcomes	Comments
	BMI range in kg/m^2: 18.5 to 40 Parity (n, %): Primiparous: Intervention group: 661 (62.4) Control group: 556 (53.6)	recommendations of the "Healthy Start – Young Family Network"			
Holmes 2017 Uncontrolled before-and-after study Northern Ireland	N = 249 Women with pregestational diabetes who gave birth or were expected to give birth between February 2012 and January 2013, and attended a joint diabetes-antenatal clinics Mean age in years (SD): Pre DVD: 30.9 (6.5) Viewed DVD: 32.0 (4.7) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Nulliparous: Pre DVD: 52 (45.6) Viewed DVD: 23 (39.7) Mean diabetes duration (SD) year Pre DVD: 12.0 (8.5) Viewed DVD: 15.6 (8.8)	Preconception counselling DVD (post-DVD cohort) Forty five minutes information on the importance of planning for pregnancy and on essential planning advice. No further information on folic advice reported in the study.	Historical cohort, (pre-DVD comparison cohort) Usual care pre implementation of preconception counselling DVD	• Preconception folic acid supplementation uptake measured at 5 months	Study adjusted for diabetes type, diabetes duration, parity, social deprivation, age and booking hospital.

Study	Population	Intervention	Comparison	Outcomes	Comments
Morgan 2009 Uncontrolled before-and-after study USA	N = 500 Non-pregnant females able to have children Mean age in years (SD): Not reported Age (n, %), years: <25: 163 (51.6) 25-34: 110 (34.8) >34: 43 (13.6) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported	400µg folic acid and verbal counselling Free multivitamin containing 400 micrograms folic acid, verbal counselling, provision of written materials explaining the importance of folic acid and free refill of folic acid vitamin when finished	Before intervention	• Folic acid supplementation uptake at 8 to 10 months follow-up	Study did not adjust for confounders
Murphy 2010 Uncontrolled before-and-after study UK	N = 680 Women with type 1 and type 2 diabetes Mean age in years (SD): Not reported Age (median years, 10-90th centile) Intervention group (women who attended pre-pregnancy counselling (PPC)): 32 (26-39) Intervention group (women who did not attend PPC): 31 (22-39) Mean BMI in kg/m^2 (SD):	Pre-pregnancy care (PPC) Leaflets were sent to women and relevant health centres disseminated relevant information regarding pre-pregnancy care. No further information on folic acid advice reported in the paper.	No pre-pregnancy care (Historical cohort) Historical cohort from same centres who did not receive pre-pregnancy care	• 5 mg folic acid supplementation uptake at 3 months follow-up	No adjustments for confounders for the reported outcome

Study	Population	Intervention	Comparison	Outcomes	Comments
	Not reported BMI at booking (median kg/m^2, 10-90th centile) Intervention group (women who attended PPC): 26.1 (21.3-36.2) Intervention group (women who did not attend PPC): 27.9 (22.2-38.1) Parity (n, %): Not reported				
Schwarz 2008 Randomised controlled trial USA	N = 446 Mean age in years (SD): Not reported Age range in years: 18 to 45 Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported	Computerised counselling about periconception folate supplementation (including folic acid supply) A 15-minute module comprising video answers to 9 folate-related questions and 200 tablet bottle of 400 micrograms folate with written instructions to take 1 tablet daily	Computerised counselling about emergency contraception A computer module on emergency contraception and a sample of emergency contraception tablets	• Change in knowledge about folate supplementation at 6 months follow-up	
Tripathi 2010 Retrospective cohort study UK	N = 588 Singleton pregnancies Mean age in years (SD): 29 (6.3) Mean BMI in kg/m^2 (SD): Not reported	Preconception counselling No additional details provided	No Preconception counselling No additional details provided	• Folic acid supplementation uptake at post-conception ○	Study adjusted for type of diabetes, IMD score, ethnicity, age at delivery, and hospital of booking

Study	Population	Intervention	Comparison	Outcomes	Comments
	Parity (n, %): Primipara: 208 (36)				
Van Dijk 2020 Randomised controlled trial The Netherlands	N = 218 Women contemplating pregnancy or <13 weeks pregnant Mean age in years (SD): Not reported Median age in years (IQR): Intervention: 30.6 (5.3) Control: 30.7 (5.7) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported Median BMI in kg/m^2 (IQR): Intervention 24.2 (6.0) Control: 23.7 (5.4) Parity (n, %): Not reported Pregnant at enrolment (n, %) Intervention: 36 (33) Control 37 (33.9)	Full version of Lifestyle change intervention program All functionality of the program and personalised interaction which involved tailored coaching on fruit, vegetables and folic acid supplement intake (a maximum of 3 emails or text messages weekly containing seasonal recipes, incentives, feedback, recommendations and additional questions regarding participants' diet)	Limited version of Lifestyle change intervention program Limited functionality and no personalised interaction	• Folic acid supplementation uptake at 6 weeks post-conception	
Van Dijk 2016 Controlled before-and-after study	N = 1525 (women only) Women (and men) contemplating pregnancy or	Smarter Pregnancy Platform 6 months of coaching on the most prevalent	Compared to control in a before-and-after study design.	• Folic acid supplementation uptake at 6 weeks follow-up (data was only reported after the intervention at the	Study did not adjust for confounders

Study	Population	Intervention	Comparison	Outcomes	Comments
The Netherlands	pregnant couples Study characteristics were reported for women who completed or stopped the smarter pregnancy platform: Mean age in years (SD): Not reported Median age in years (IQR) Completed: 31.2 (27.7-34.6) Stopped: 31.5 (27.9-35.2) Mean BMI in kg/m^2 (SD): Not reported Median BMI in kg/m^2 (IQR) Completed: 24.0 (21.3-27.6) Stopped: 24.0 (21.7-27.0) Parity (n, %): Not reported No folic acid intake (n, %): Completed: 150 (14.96) Stopped: 72 (13.8) Pregnant (n, %): Completed: 416 (41.48) Stopped: 187 (35.9) Study cohort (N=1525)	inadequate nutrition and lifestyle behaviours (that is, vegetable, fruit, and alcohol intake) or the most strongly demonstrated associations of behaviours with fertility and pregnancy course and outcome (that is, tobacco and folic acid supplement use).	The comparison was the Smarter Pregnancy Platform group prior to receiving coaching.	time of follow-up with no information reported on uptake at baseline (control group))	

Study	Population	Intervention	Comparison	Outcomes	Comments
	included women with adequate and inadequate nutrition and lifestyle behaviours but coaching was only delivered to the subgroup of the population with inadequate behaviours (n=222) at baseline and data was only provided for this subgroup.				
Watkins 2004 Prospective cohort study USA	N = 165 Women visiting family planning clinics Mean age in years (SD): Not reported Age (n, %) in years in years: Pill intervention: 18-35: 58 (85.3) 36-45: 10 (14.7) Education only: 18-35: 17 (70.8) 36-45: 7 (29.2) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported	Pill intervention 400 micrograms folic acid supplements and educational material about folic acid	Education only intervention Folic acid brochure designed for women not contemplating pregnancy	• Folic acid supplementation uptake measured at 1 year follow-up • Change in knowledge measured at 1 year follow-up	Study adjusted for visit number, intervention type, age, race/ethnicity, and education. Knowledge about folic acid and smoking status were included as covariates for the outcome folic acid supplementation uptake
Yamamoto 2018	N = 831	Pre-pregnancy care (PPC) program	No pre-pregnancy care program	• Folic acid supplementation uptake measured after intervention	Study did not adjust for confounders

Study	Population	Intervention	Comparison	Outcomes	Comments
Uncontrolled before-and-after studies UK	Women with type 1 or type 2 diabetes Mean age in years (SD), type 1 diabetes: After pre-pregnancy care (PPC): 30.2 (5.8) Before PPC: 31.2 (5.9) Mean age in years (SD), type 2 diabetes After PPC: 33.4 (5.4) Before PPC: 34.7 (5.2) Mean BMI in kg/m^2 (SD): Not reported Parity (n, %): Not reported	Distribution of printed and electronic copies of a pre-pregnancy care leaflet, preconception care templated embedded into electronic care records with alerts for healthcare professionals to promote its use during visits and advice for women to take 5 mg folic acid daily	Historical cohort of women before the pre-pregnancy care program	(follow-up not reported)	

BMI: Body mass index; CDC: Centres for Disease Control and Prevention; DVD: digital versatile disc; IMD: index of multiple deprivation; IQR: interquartile range; kg: kilograms; m: metres; n: number of participants; NR: not reported; NTDs: neural tube defects; PPC: pre-pregnancy care; SD: standard deviation; USA: United States of America; WIC: Women, Infants, and Children's special supplemental nutrition program.

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

Summary of the evidence

The below paragraphs summarise the evidence for these comparisons:

- folic acid information/education provision versus status quo treatment (including no treatment), by following strata:
  - in women with BMI thresholds in the overweight or obese range
  - in women without comorbidities
  - in women with comorbidity (diabetes)
- folic acid focused information/education provision versus limited information/education provision, mixed strata
- multicomponent interventions of folic acid information/education provision and folic acid supply versus control (before intervention), mixed strata
- multicomponent interventions of folic acid information/education provision versus another multicomponent intervention of general information/education provision and folic acid supply, mixed strata

- multicomponent intervention of folic acid information/education provision and folic acid supply versus another multicomponent intervention of emergency contraception information/education provision and emergency contraception supply, mixed strata
- multicomponent intervention of folic acid information/education provision and folic acid supply versus folic acid information/education provision only, mixed strata.

Comparison 1: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with BMI thresholds in the overweight or obese range (Mixed strata for folic acid supplementation dose, age, deprived socioeconomic group and comorbidities) – combined components

One controlled before and after study including women with BMI thresholds in the overweight or obese range was included in this comparison. For the outcome of folic acid supplementation uptake (all doses), clinical importance could not be assessed due to insufficient information provided in the paper to assess changes from baseline.

The quality of the evidence was very low.

Comparison 2: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women without comorbidities (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – combined components

One controlled before and after study including women without comorbidities was included in this comparison. For the outcome folic acid supplementation uptake (all doses), clinical importance could not be assessed due to insufficient information provided in the paper to assess changes from baseline.

The quality of the evidence was very low.

Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – combined components

One retrospective cohort study and 4 uncontrolled before and after studies were included in this comparison.

Evidence for interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) suggested mixed findings for folic acid supplementation uptake (all doses; important benefit or no evidence of important differences) and 5 mg folic acid supplementation uptake (possible important benefit or no evidence of important differences). However, when potential confounders were adjusted for, there was a possible important benefit for 5 mg folic acid supplementation uptake and important benefit for folic acid supplementation uptake (all doses).

The quality of the evidence was very low.

Sensitivity analysis for comparison 3: intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group)

Three uncontrolled before-and-after studies were included in this sensitivity analysis.

Sensitivity analysis could not be conducted for components 2, 3 and 7 of the interventions in this comparison as there was insufficient information from one study and in the other 2 studies the components were the same for the same outcome.

Sensitivity analysis for component 1: mode of delivery

Evidence for interventions using information/education provision with mode of delivery as face to face versus status quo (including no treatment) in women with comorbidities (diabetes) suggested an important benefit for folic acid supplementation uptake (all doses) at 8 weeks follow-up and 5mg folic acid supplementation uptake at 3 months follow-up.

Evidence for interventions using information/education provision with mode of delivery as printed and digital/electronic interventions versus status quo (including no treatment) in women with comorbidities (diabetes) suggested no important difference for folic acid supplementation uptake (all doses; follow up not reported) and 5mg folic acid supplementation uptake (follow-up not reported).

The quality of the evidence was very low.

Sensitivity analysis for component 4: individualised/tailored or general interventions

Evidence for interventions using information/education provision with on demand, tailored interventions based on needs versus status quo (including no treatment) in women with comorbidities (diabetes) suggested an important benefit for folic acid supplementation uptake.

There was no important difference for interventions using information/education provision with general interventions aimed at the population of interest versus status quo (including no treatment) in women with comorbidities (diabetes) for folic acid supplementation uptake (all doses).

The quality of the evidence was very low.

Sensitivity analysis was not carried out for component 4 of the intervention for the outcome 5mg folic acid supplementation as the components (general intervention, aimed at the population of interest) were the same in both studies.

Sensitivity analysis for component 5: who delivers the intervention?

Evidence for interventions using information/education provision delivered by healthcare practitioners, health or social care workers (consultant obstetricians, consultant physician, diabetes specialist nurse and a dietician) versus status quo (including no treatment) in women with comorbidities (diabetes) suggested an important benefit for folic acid supplementation uptake (all doses) at 8 weeks follow-up. The evidence suggests an important benefit for interventions using information/education provision delivered by healthcare practitioners, health or social care workers (diabetes physician, specialist nurse, midwife, or obstetrician) when compared with status quo for the outcome 5mg folic acid supplementation at 3 months follow-up in women with comorbidities (diabetes).

There was no important difference for interventions using information/education provision delivered by healthcare practitioner, health or social care worker (specialist antenatal diabetes team) versus status quo (including no treatment) in women with comorbidities (diabetes) for folic acid supplementation uptake (all doses; follow-up not reported) and 5mg folic acid supplementation uptake (follow-up not reported).

The quality of the evidence was very low.

Sensitivity analysis for component 6: where the intervention was delivered?

Evidence for interventions using information/education provision delivered in specialist clinics versus status quo (including no treatment) in women with comorbidities (diabetes) suggested an important benefit for folic acid supplementation uptake (all doses) and 5mg folic acid supplementation uptake at 3 months follow-up.

There was no important difference for interventions using information/education provision delivered during consultation with healthcare professionals or health and social care worker

versus status quo (including no treatment) in women with comorbidities (diabetes) for folic acid supplementation uptake (all doses) and 5mg folic acid supplementation uptake (follow-up not reported).

The quality of the evidence was very low.

Comparison 4: Intervention group 1: Focused interventions using information/education provision versus limited information/education provision (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities)

Two randomised controlled studies (one cluster randomised controlled trial) were included in this comparison.

Interventions using focused information/education provision showed no evidence of important differences over limited information/education provision for folic acid supplementation uptake.

The quality of the evidence was very low.

Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Four uncontrolled before and after studies were included in this comparison.

Overall, multicomponent interventions involving information/education provision and supply of folic acid showed mixed findings (that is, both important benefit or no evidence of important differences) when compared with before the intervention for folic acid supplementation uptake (all doses). For change in knowledge, there was no evidence of important differences for multicomponent interventions before and after the intervention.

The quality of the evidence was very low.

Sensitivity analyses for comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities)

Sensitivity analysis was not conducted for components 2, 4 and 7 of the interventions in this comparison as the components were the same across the pooled studies for the same outcome.

Sensitivity analysis for component 1: mode of delivery

Three uncontrolled before-and-after studies were included in this comparison.

Multicomponent interventions involving information/education provision and supply of folic acid delivered face-to face together with printed materials and face-to-face together with a digital/electronic element (telephone) showed an important benefit for folic acid supplementation uptake (follow-up at 4 months or at 8 to 10 months) when compared with before the intervention.

For change in knowledge of folic acid, multicomponent interventions involving information/education provision and supply of folic acid delivered face-to-face along with a digital/electronic element showed mixed findings (that is, important benefit or no evidence of important differences) and multicomponent interventions involving information/education provision and supply of folic acid delivered face-to-face along with printed materials showed no important difference.

The quality of the evidence was very low.

Sensitivity analysis for component 3: interventions aimed at individuals or groups

Two uncontrolled before and after studies were included in this comparison.

Multicomponent interventions involving information/education provision and supply of folic acid aimed at individuals and aimed at groups both showed an important benefit for folic acid supplementation uptake (follow-up at 4 months or at 8 to 10 months) when compared with before the intervention.

The quality of the evidence was very low.

Sensitivity analysis was not carried out for component 3 of the intervention for the outcomes Change in knowledge: Knowledge that folic acid prevents birth defects and Change in knowledge: Knowledge that folic acid is important to women of childbearing age as the components (interventions aimed at groups) were the same in both studies.

Sensitivity analysis for component 5: who delivers the intervention

Two uncontrolled before and after studies were included in this comparison.

Multicomponent interventions involving information/education provision and supply of folic acid when delivered by healthcare practitioners, health or social care workers such as nurses, or by a folic acid supplementation 'champion' showed an important benefit for folic acid supplementation uptake (follow-up at 4 months or at 8 to 10 months) when compared with before the intervention.

The quality of the evidence was very low.

Sensitivity analysis was not carried out for component 5 of the intervention for the outcomes Change in knowledge: Knowledge that folic acid prevents birth defects and Change in knowledge: Knowledge that folic acid is important to women of childbearing age as the components (folic acid supplementation 'champion' - promotora) were the same in both studies. .

Sensitivity analysis for component 6: where the intervention is delivered

Three uncontrolled before and after studies were included in this comparison.

Multicomponent interventions involving information/education provision and supply of folic acid when delivered during consultation with a healthcare professional showed an important benefit when compared with before the intervention for folic acid supplementation uptake. Multicomponent interventions involving information/education provision and supply of folic acid when delivered at other locations such as community centres, and churches showed mixed findings (important benefit, no important difference or no evidence of important differences) for change in knowledge of folic acid.

The quality of the evidence was very low.

Comparison 6: Intervention group 5: Multicomponent interventions (focused information/education provision and folic acid supply) versus control (unfocused information/education provision and folic acid supply) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

One randomised controlled trial was included in this comparison.

Multicomponent interventions involving focused information/education provision and folic acid supply compared to control (unfocused information/education provision and folic acid supply) showed an important benefit for multicomponent interventions involving focused information/education provision for the outcome of folic acid supplementation uptake (all doses).

The quality of the evidence was low.

Comparison 7: Intervention group 5: Multicomponent interventions (folic acid information/education provision and folic acid supply) versus multicomponent intervention control (emergency contraception (EC) information/education provision and EC supply) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

One randomised controlled trial was included in this comparison.

Multicomponent interventions involving general folic acid information/education provision and folic acid supply showed an important benefit for the outcomes of both folic acid supplementation uptake and change in folic acid knowledge when compared to multicomponent intervention control (emergency contraception (EC) information/education provision and EC supply).

The quality of the evidence was moderate to low.

Comparison 8: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus information/education provision only (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

One prospective cohort study was included in this comparison.

Multicomponent interventions involving general information/education provision and folic acid supply showed important benefit over information/education provision only for the outcome of folic acid knowledge after adjusting for important confounders. Multicomponent interventions involving general information/education provision and folic acid supply when compared to information/education provision only did not show evidence of important difference for the outcome of folic acid supplementation uptake after adjusting for important confounders.

The quality of evidence was low to very low.

See appendix F for full GRADE tables.

Economic evidence

Included studies

Five economic studies were identified which were relevant to this question (Dalziel 2010, de Weerd 2004, Filby 2015, Grosse 2008, Postma 2002).

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

Excluded studies

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

1 Summary of included economic evidence

2 See Table 3 for the economic evidence profile of the included studies.

Table 3: Economic evidence profile for periconceptional folic acid supplementation versus standard care levels of folic acid uptake

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
Dalziel 2010 Australia	Potentially serious[2]	Partially applicable[3]	Interventions: Promotion of folic acid supplementation 1 month prior to and 3 months following conception through: a. General campaign ["General"] b. Targeted campaign to disadvantaged women ["Targeted"] c. Brief clinician advice to women aged 18-48 years ["Clinical advice"] Outcome: number of NTDs prevented number of DALYs averted Time horizon: 10 years for costs, lifetime for outcomes Cost year: 2006	General: £10,169,197 Targeted: £994,337 Clinical advice: £2,020,688	Total NTDs prevented: General: 21.0 Targeted: 3.9 Clinical advice: 10.1 Total DALYs averted: General: 2,243 Targeted: 163 Clinical advice: 1,080	Cost/NTD prevented: General: £27,265 Targeted: £29,991 Clinical advice: £11,451 Cost/DALY averted: General: £4,511 Targeted: £6,097 Clinical advice: £1,884	Cost/DALY averted (range in SA): General: £1,636-£9,369 Targeted: £2,379-£10,856 Clinical advice: £248-£4,957
De Weerd 2004 The Netherlands	Potentially serious[4]	Partially applicable[5]	Interventions: Preconception counselling by a GP about folic acid supplementation vs no intervention Outcome: number of NTDs averted Time horizon: 1 year Cost year: 2002	• 50% uptake: £15 • 75% uptake: £23	50% uptake: 0.0001 75% uptake: 0.0002	50% uptake: £138,000 75% uptake: £127,500	NR

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
			Separate costs provided according to intervention uptake				
Filby 2015 UK	Potentially serious[6]	Directly applicable[7]	Populations: (1) women planning a pregnancy and pregnant women <10 weeks (2) pregnant women <10 weeks Interventions: Universal offering of Healthy Start Vitamin programme to all women planning a pregnancy and pregnant women (<10 weeks) Current scheme: No offering of Healthy Start Vitamin programme to all women planning a pregnancy and pregnant women <10 weeks Outcome: QALY Time horizon: lifetime for NTDs Cost year: 2014	For women planning a pregnancy and those <10 weeks pregnant: -£0.89 For pregnant women <10 weeks: £2.35	For women planning a pregnancy and those <10 weeks pregnant: 0.000663 For pregnant women <10 weeks: 0.000320	For women planning a pregnancy and those <10 weeks pregnant: dominant For pregnant women <10 weeks: £7,126	NR
Grosse 2008 US	Potentially serious[8]	Partially applicable[9]	Population: women with a pregnancy affected by NTD Interventions: counselling and free folic acid supplements directly to women with a prior NTD-affected pregnancy identified through a birth defect–surveillance system vs standard care (no intervention following identification) Outcome: QALY	NR	NR	£10,231	£2,837 to £37,258

Study and country	Limitations	Applicability	Other comments	Incremental costs[1]	Incremental effects	ICER[1]	Uncertainty
			Time horizon: lifetime Cost year: 2003				
Postma 2002 The Netherlands	Potentially serious[10]	Partially applicable[11]	Interventions: Periconceptional supplementation of folic acid, recommended by gynaecologists (0.5 mg/day) [assuming effectiveness of 50% uptake] vs standard care [assuming 0% uptake] Outcome: number of life years gained Time horizon: lifetime Cost year: 2000	NR	NR	£1,516	In SA ICER ranged from intervention being dominant to £5,470

DALY: disability-adjusted life year; DSA: Deterministic sensitivity analysis; ICER: Incremental cost-effectiveness ratio; NR: not reported; NTD: neural tube defect; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life year; SA: Sensitivity analysis

1 Costs converted to GBP using Purchasing Power Parity exchange rates

2 Study based on decision-analytic modelling; effectiveness and costs based on seminal and other published studies; national unit costs used; 10-year horizon for costs, lifetime for outcomes; DSA conducted.

3 Australian study, DALYs used, healthcare perspective (& public sector where relevant for intervention delivery), discounting: 5% annually

4 Study based on decision-analytic modelling; effectiveness based on literature review; costs taken from published evidence and hospital records; 1-year time horizon; no SA conducted.

5. Dutch study, QALYs were not used, healthcare perspective, discounting not needed

6 Study based on decision-analytic modelling; effectiveness and costs based on published study, national surveys and a primary online survey, government and local data, other published evidence; national and local unit costs used; lifetime horizon; no DSA conducted for this analysis.

7 UK study, QALYs used, perspective NHS and public (local and central government), discounting 3.5%

8 Study based on decision-analytic modelling; effectiveness based on literature review; costs taken from administrative records and published evidence; lifetime horizon; best and worst-case scenario SA conducted.

9 US study, QALYs used, societal perspective (healthcare – education – other services – patient – productivity losses), discounting: 3% annually

10 Study based on decision-analytic modelling; effectiveness based on literature review; costs mainly taken from a published US study and national data; lifetime horizon; total costs and outcomes per arm or incremental costs and outcomes not reported separately; DSA and PSA conducted.

11 Dutch study, QALYs were not used, perspective: healthcare & special education, discounting: 4% annually

Economic model

This area was prioritised for de novo economic modelling. The committee selected to assess the cost-effectiveness of health technologies (such as apps), because these are the only interventions they considered for a recommendation which have promising evidence but are not currently in routine use in England. However, there was no adequate effectiveness evidence on health technologies to allow a meaningful and informative economic analysis to be carried out. Therefore, no economic model was developed for this review question.

Economic evidence statements

- Evidence from 1 UK modelling study suggests that universal offering of the Healthy Start Vitamin programme to all women planning a pregnancy and/or pregnant women below 10 weeks in pregnancy is likely to be cost-effective compared with current scheme, according to which the Healthy Start Vitamin programme is not offered to these populations. The evidence is directly applicable to the UK context and is characterised by potentially serious limitations.
- Evidence from 1 US modelling study suggests that counselling and free folic acid supplements directly to women with a prior NTD-affected pregnancy identified through a birth defect–surveillance system is likely to be cost-effective compared with standard care (no intervention following identification). The evidence is partially applicable to the UK and is characterised by potentially serious limitations.
- Evidence from 1 Australian modelling study was unclear as to whether promotion of folic acid supplementation 1 month prior to and 3 months following conception through a general campaign, a targeted campaign to disadvantaged women or brief clinician advice to women aged 18-48 years was cost-effective compared with no intervention, as the study did not use the QALY as the measure of outcome, so it was difficult to assess whether additional benefits (number of NTDs or DALYs averted) were worth the extra costs incurred. The evidence is partially applicable to the UK and is characterised by potentially serious limitations.
- Evidence from 2 Dutch modelling studies was unclear as to whether preconception counselling by a GP about folic acid supplementation or periconceptional supplementation of folic acid, recommended by gynaecologists (0.5 mg/day) vs standard care were cost-effective compared with no intervention, as the studies did not use the QALY as the measure of outcome, so it was difficult to assess whether additional benefits (number of NTDs averted and number of years gained, respectively) were worth the extra costs incurred. The evidence is partially applicable to the UK and is characterised by potentially serious limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Folic acid supplementation uptake was prioritised as the critical outcome by the committee because it is the most appropriate measure that directly answers the review question. The committee considered that both subjective and objective measures of folic acid supplementation uptake will be useful to determine the effectiveness of any interventions aimed at improving uptake of folic acid.

The committee agreed that changes in attitude, confidence and knowledge as part of people's intention to change behaviour and unintended consequences such as supplementation wastage and increase in inequalities should be important outcomes. This was because they are common factors to measure and target in an intervention and can ultimately impact on behaviour.

No evidence was found that reported on the outcomes of changes in attitude and confidence, and unintended consequences such as supplementation wastage and increase in inequalities.

The quality of the evidence

The quality of the evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology. The quality of the evidence was largely of very low quality. The main reasons for downgrading were risk of bias, inconsistency, imprecision and indirectness. For randomised controlled studies, there was risk of bias from the randomisation process and deviation from intended intervention for some studies, otherwise risk of bias was commonly due to issues with missing outcome or measurement of outcome. For prospective cohort studies, retrospective cohort studies, controlled before-and-after studies and uncontrolled before-and-after studies, risk of bias was most commonly due to issues with lack of adjustment for confounding, measurement of outcomes and missing outcome data. There was substantial variation in the quality and completeness of descriptions of the interventions and comparators between the studies, which may be a possible reason for the inconsistency observed for some outcomes. Imprecision could not be assessed for one study (Van Dijk 2020) as the study reported the estimates as beta coefficient. One study was downgraded for indirectness as the intervention focused on decreasing the proportion of women who gained excessive weight during pregnancy but included information on folic acid uptake.

Individual studies were assessed for methodological quality based on their study design. Randomised trials were assessed using the Cochrane Risk of bias (RoB) 2.0 tool, cluster randomised studies were assessed using the Cochrane RoB 2.0 tool for cluster randomised trials, cohort studies and uncontrolled before-and-after studies were assessed using the Risk of Bias in Non-randomised Studies of Interventions (ROBINS-I) tool, and controlled before-and-after studies were assessed using the Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias tool.

Benefits and harms

The committee reviewed the evidence on interventions using information provision and multicomponent interventions to increase the uptake of government advice on folic acid supplements. The committee noted the diversity of the interventions included in the review in terms of the components, duration, intensity and mode of delivery of the programmes. The review findings were discussed along with the qualitative evidence on facilitators and barriers to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy to inform the recommendations (evidence report P).

The current UK guidance recommends that folic acid supplementation to prevent NTDs should be taken before becoming pregnant and for the first 12 weeks of pregnancy, but uptake of the supplementation is quite low. The committee were interested to know if and what type of interventions in the preconception period could be effective. Most of the included studies had interventions which were delivered during the preconception period, and some had interventions delivered in early pregnancy or in the post-partum period. There was evidence, although generally very poor in quality, that showed an important benefit or possible important benefit for folic acid uptake and change in knowledge when the intervention was delivered in the preconception or post-natal period. The interventions where either information/education provision alone or together with provision of folic acid supplement. Based on the limited evidence and the qualitative evidence in evidence review P, the committee agreed that information about the importance of folic acid supplementation before pregnancy, in early pregnancy and in the post-partum period should be readily available in different healthcare settings so people who may become pregnant can receive this information (for example via posters, leaflets). The committee agreed, based on consensus, examples of these settings. See further discussion in evidence review P.

The committee also agreed that in addition to the information being readily available in different settings, there should also be proactive engagement with and information provision for people attending healthcare services who may become pregnant or who are already pregnant. The committee discussed that obviously not all people of reproductive age are planning pregnancy or becoming pregnant but there are some healthcare contacts were discussing or sharing information about folic acid supplementation can be more relevant and effective, such as appointments related to contraception, sexual health, pregnancy planning and preconception health, fertility, antenatal care, postnatal care and child health (for future pregnancies).

The committee considered the components of the interventions reviewed in the evidence and agreed that it seemed that information/education provision aimed at both individuals and groups seemed to show some benefit in folic acid uptake, as well as information/education provided face-to-face or remotely (telephone). The committee therefore agreed to recommend that the importance of folic acid should be discussed with anyone who may become pregnant, is planning pregnancy or is already pregnant attending appointments or sessions related to the above topics. These could be face-to-face, telephone or virtual appointments or group sessions. Based on the qualitative evidence, the committee also emphasised that this is important regardless of the person's parity or pregnancy history.

The committee agreed that the information provision during these contacts should include the government advice about folic acid, including the reason for taking folic acid supplements (to prevent NTDs and other congenital malformations) and the recommended timeline for taking the supplements (ideally 3 months before conception or as soon as possible after a positive pregnancy test and at least up to 12 weeks of pregnancy). The committee discussed the 2021 decision by the government to fortify white flour with folic acid (which to date has not yet been implemented). The committee acknowledged that due to the publicity of these plans, many people may have become aware of this, which may lead to a reduced intake of folic acid supplements once the plans are implemented. The committee noted that dietary folate intake alone is not sufficient to provide the amount of folic acid required daily so they agreed that information provision should include the importance of taking folic acid supplementation even if consuming foods fortified with folic acid. Further discussion points based on the qualitative evidence are discussed in evidence review P.

The committee discussed based on their knowledge and experience and the qualitative evidence (see evidence report P) that there are various reasons why uptake of folic acid supplementation is low despite efforts to raise awareness about it. The committee discussed that when it is known that someone is not taking the recommended folic acid supplementation, targeted information and support or reminders are needed to encourage uptake, and these could be through digital technologies (such as apps) which are becoming more common in healthcare services. However, there was limited evidence for the use of digital or health technology interventions in this review to establish its effectiveness in delivering interventions to increase folic acid uptake, so the committee made a research recommendation to assess the effectiveness of digital technologies in increasing the uptake of folic acid supplementation before and during the first 12 weeks of pregnancy. See appendix K for more details.

The committee considered the evidence on women with existing comorbidities but only evidence on women with diabetes was available. The committee did not think a specific recommendation for this group is needed in relation to interventions to increase uptake of folic acid supplements. The committee noted that high dose of folic acid is recommended for this group and that there is an expectation that those with diabetes are already accessing specialist services where information about folic acid supplementation should be offered as part of those services. The committee also considered the evidence for women medically classified as overweight or obese and did not think the evidence warranted a specific recommendation for this group.

Additionally, the committee would have been interested to find evidence on women from lower socioeconomic backgrounds who may not have the same level of access to folic acid supplements or may have other reasons why uptake is low. There was no evidence in this review to make recommendations based on socioeconomic status. However, the committee agreed to include subgroups of people with different socioeconomic backgrounds in the research recommendation on digital technologies. See appendix K for more details.

There was no evidence in the review to make specific recommendations based on age (under and over 40 years of age), women with disabilities (including learning disabilities) and other physical and mental health conditions, women going through assisted conception, LGBTQ+ women, geographical variation and ethnicity. Hence the committee included these sub-groups in the research recommendation. See appendix K for more details.

Cost effectiveness and resource use

There was evidence from UK that universal offering of the Healthy Start Vitamin programme to all women planning a pregnancy and/or pregnant women up to 10 weeks of pregnancy was likely to be cost-effective compared with current offering of the scheme, as it increased the uptake of folic acid in this population and thus resulted in fewer pregnancies affected by neural tube defects. Universal offering of the programme to this population was cost-effective only if the cost per head of including women planning a pregnancy and those who are less than 10 weeks pregnant was not considerably higher than the cost per head for women already in the scheme. However, a mechanism would need to be identified to deliver a universal scheme to these 2 groups, which would require a new route to target women this early on.

Moreover, US evidence suggested that counselling and supplying free folic acid supplements directly to women with a prior pregnancy affected by neural tube defects was likely to be cost-effective. Other non-UK evidence was unclear as to whether periconceptual promotion, counselling and/or supplementation of folic acid was cost-effective within the NICE decision-making context, owing to lack of use of the QALY as the measure of outcome. The review question was originally prioritised for economic modelling, as the committee wished to assess the cost-effectiveness of health technologies in enhancing uptake of folic acid. However, clinical evidence around health technologies was too limited and uncertain to inform an economic model. The recommendations made reflect mostly current practice and aim to reiterate government advice and harmonise practice across a range of healthcare settings by provision of advice during routine or other planned appointments. Moderate resource implications (in terms of health professionals' time) are expected in settings where optimal advice on folic acid supplementation is currently not offered or is limited. On the other hand, the recommendation to provide targeted information, support and follow-up reminders (including health technologies if available) on folic acid supplementation to those not taking the recommended folic acid supplement is anticipated to have potentially important resource implications regarding healthcare professionals' time. The committee noted that the recommendation is focused on a targeted population that has been identified as not taking the recommended folic acid supplement, rather than the whole population that is planning to become pregnant or is already pregnant, so that resource implications are more limited, and that the benefits (and cost-savings) of preventing pregnancies affected by neural tube defects in this population are likely to outweigh the cost of reminders. On the other hand, it is acknowledged that, currently, compliance with current guidance on folic acid supplementation in the population is low, therefore the recommendation involves a large part of the population that is planning to become pregnant or is already pregnant. The recommendation refers to the option of health technologies only where these are already available, as the committee acknowledged the cost associated with setting up new health technology systems, the limited clinical evidence favouring health technologies that are used to disseminate information and advice on folic acid supplementation, but also the lack of economic evidence around their use.

Other factors the committee took into account

For this review question, in relation to folic acid supplementation before, during or after pregnancy, 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 1.1.1 to 1.1.3 and 1.1.8 and the research recommendation on digital technologies to increase uptake of folic acid supplementation. Other evidence supporting these recommendations can be found in the evidence review P on facilitators and barriers to increase the uptake of government advice on folic acid and vitamin supplements.

References – included studies

Effectiveness

Anwar 2011

Anwar, Ayesha, Salih, Amira, Masson, Ewan et al. The effect of pre-pregnancy counselling for women with pre-gestational diabetes on maternal health status. European journal of obstetrics, gynecology, and reproductive biology 155(2): 137-9, 2011

Chilukuri 2018

Chilukuri, Nymisha, Cheng, Tina L, Psoter, Kevin J et al. Effectiveness of a Pediatric Primary Care Intervention to Increase Maternal Folate Use: Results from a Cluster Randomized Controlled Trial. The Journal of pediatrics 192: 247-252e1, 2018

de Weerd 2002

de Weerd, S, Thomas, CMG, Cikot, RJL et al. Preconception counseling improves folate status of women planning pregnancy. Obstetrics & Gynecology 99(1): 45-50, 2002

deRosset 2014

deRosset, Leslie, Mullenix, Amy, Flores, Alina et al. Promotora de Salud: Promoting Folic Acid Use Among Hispanic Women. Journal of Women's Health (15409996) 23(6): 525-531, 2014

Flores 2017

Flores, Alina L., Isenburg, Jennifer, Hillard, Christina L. et al. Folic Acid Education for Hispanic Women: The Promotora de Salud Model. Journal of Women's Health (15409996) 26(2): 186-194, 2017

Geyer 2022

Geyer, K., Gunther, J., Hoffmann, J. et al. Dietary Supplementation Before, during and after Pregnancy: Results of the Cluster-Randomized GeliS Study. Geburtshilfe und Frauenheilkunde 82(7): 736-746, 2022

Holmes 2017

Holmes, V.A., Hamill, L.L., Alderdice, F.A. et al. Effect of implementation of a preconception counselling resource for women with diabetes: A population based study. Primary Care Diabetes 11(1): 37-45, 2017

Morgan 2009

Morgan. LM, Major J, Meyer R et al. Multivitamin use among non-pregnant females of childbearing age in the Western North Carolina multivitamin distribution program. N C Med J 5(70): 386-90, 2009

Murphy 2010

Murphy, H.R., Roland, J.M., Skinner, T.C. et al. Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: Benefits beyond glycemic control. Diabetes Care 33(12): 2514-2520, 2010

Schwarz 2008

Schwarz, Eleanor Bimla, Sobota, Mindy, Gonzales, Ralph et al. Computerized counseling for folate knowledge and use: a randomized controlled trial. American journal of preventive medicine 35(6): 568-571, 2008

Tripathi 2010

Tripathi, A, Rankin, J, Aarvold, J et al. Preconception counseling in women with diabetes: a population-based study in the north of England. Diabetes Care 33(3): 586-588, 2010

van Dijk 2020

van Dijk, M.R., Koster, M.P.H., Oostingh, E.C. et al. A mobile app lifestyle intervention to improve healthy nutrition in women before and during early pregnancy: Single-center randomized controlled trial. Journal of Medical Internet Research 22(5): e15773, 2020

van Dijk 2016

Van Dijk, Matthijs R, Huijgen, Nicole A, Willemsen, Sten P et al. Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey. JMIR mHealth and uHealth 4(2): e53, 2016

Watkins 2004

Watkins M; Brustrom J; Schulman J Effectiveness of a free folic acid supplement program in family planning clinics. Birth Defects Res A Clin Mol Teratol 6: 403-7, 2004

Yamamoto 2018

Yamamoto, J.M., Hughes, D.J.F., Evans, M.L. et al. Community-based pre-pregnancy care programme improves pregnancy preparation in women with pregestational diabetes. Diabetologia 61(7): 1528-1537, 2018

Economic

Dalziel 2010

Dalziel K, Segal L, Katz R. Cost-effectiveness of mandatory folate fortification v. other options for the prevention of neural tube defects: results from Australia and New Zealand. Public Health Nutr 2010; 13(4):566-78.

de Weerd 2004

de Weerd S, Polder JJ, Cohen-Overbeek TE, Zimmermann LJ, Steegers EA. Preconception care: preliminary estimates of costs and effects of smoking cessation and folic acid supplementation. J Reprod Med 2004; 49(5):338-44.

Filby 2015

Filby A, Taylor M, Jenks M, Burley V. Examining the cost-effectiveness of moving the Healthy Start Vitamin Programme from a targeted to a universal offering. Final report. York Health Economics Consortium, 2015.

Grosse 2008

Grosse SD, Ouyang L, Collins JS, Green D, Dean JH, Stevenson RE. Economic evaluation of a neural tube defect recurrence-prevention program. Am J Prev Med 2008; 35(6):572-7.

Postma 2002

Postma MJ, Londeman J, Veenstra M, de Walle HE, de Jong-van den Berg LT. Cost-effectiveness of periconceptional supplementation of folic acid. Pharm World Sci 2002; 24(1):8-11.

Other

Barbour 2012

Barbour, RS., Macleod, M., Mires, G. and Anderson, AS. Uptake of folic acid supplements before and during pregnancy: focus group analysis of women's views and experiences. Journal of Human Nutrition and Dietetics, 25: 140-147, 2012.

Stephenson 2014

Stephenson J, Patel D, Barrett G, et al. How do women prepare for pregnancy? Preconception experiences of women attending antenatal services and views of health professionals. PLoS One; 9(7): e103085, 2014.

Appendices

Appendix A Review protocols

Review protocol for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Table 4: Review protocol

Field	Content
PROSPERO registration number	CRD42022355216
Review title	Interventions to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy
Review question	What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?
Objective	To assess how effective interventions are to increase the uptake of low-dose, medium-dose and high-dose folic acid supplementation among women 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 • CINAHL • PsycInfo • International HTA database • Health Technology Assessment (HTA)

Field	Content
	Searches will be restricted by: • English language only • Human studies only 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	Uptake of low-dose (<1 mg daily); medium-dose folic (≥1 to <5 mg daily); high-dose (≥5 mg daily) folic acid supplementation in line with government advice https://www.nhs.uk/medicines/folic-acid/how-and-when-to-take-folic-acid/
Population	Inclusion: • Women trying to become pregnant before and during the first 12 weeks of a single or multiple pregnancy Exclusion: • None Note: interventions aimed at parents/carers of women will be included only if they are representing their child or charge
Intervention	**Interventions will be included if the main aim is to increase uptake of folic acid supplementation. Interventions will be organised according to the following groups:** **Intervention group 1:** Interventions using information provision and/or education **Intervention group 2:** Interventions using alternative forms of folic acid supplementation (drops or tablets)

Field	Content

	Intervention group 3: Interventions aimed at improving access to folic acid supplementation (that is, provision of folic acid supplementation in different settings or incorporation of folic acid in welfare schemes)
	
	Intervention group 4: Interventions using psychological or behavioural techniques
	
	Intervention group 5: Multicomponent interventions (interventions that combine more than 1 intervention listed above)
	
	The committee anticipated that, along with the intervention, studies would report at least 1 component of each of the groups noted below. Sensitivity analyses will be done according to these if enough data is available.
	
	• **Component 1:** Mode of delivery
	  ○ Face-to-face (in person, videoconference)
	  ○ Printed
	  ○ Digital/Electronic
	  ○ Audio
	  ○ Visual
	  ○ Textual (involving written text)
	
	• **Component 2:** When is the intervention delivered
	  ○ During the pre-conception period (that is, women trying to become pregnant)
	  ○ During the first 12 weeks of pregnancy
	
	• **Component 3:** Intervention aimed at individuals or groups
	  ○ Individual based
	  ○ Group based
	
	• **Component 4:** Individualised or tailored interventions

Field	Content
	○ On demand, tailored interventions based on needs ○ General, aimed to all the population of interest • **Component 5:** Who delivers the intervention ○ Healthcare practitioner, health or social care worker (report what type) ○ Peer (person with professional education on providing information and education on folic acid) ○ Folic acid supplementation 'champion' • **Component 6:** Where is the intervention delivered ○ During home visits ○ During consultation with healthcare professionals or health and social care workers (including opportunistic interventions) ○ At support group meetings for patients and other people who use services ○ Community pharmacies ○ Antenatal clinics ○ Specialist clinics ○ Community venues ○ Religious settings ○ Other (report what type) • **Component 7:** Behaviour change models, techniques and theories ○ trans-theoretical model (stages of change) ○ theory of planned behaviour ○ theory of reasoned action ○ health protection theory ○ protection motivation theory ○ social cognitive theory ○ perceptions of risk ○ Other (report what type)

Field	Content
	○ No theory mentioned
Comparator	• One of the above interventions (within the same group or different group interventions will be considered) • Status quo/treatment as usual (as defined by study authors, includes no treatment) • Time (before and after)
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs • If insufficient parallel RCTs*: • Quasi-randomised controlled trials • Non-randomised controlled trials/Prospective cohort studies • Retrospective cohort studies • Historically controlled studies • Ecological studies (geographical) • Controlled before-and-after studies (including before and after surveys) *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. Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	<u>Setting:</u> • Countries other than high income countries (as defined by the OECD)

Field	Content
	If any study or systematic review includes <1/3 of women who received care in the above setting, it will be considered for inclusion but, if included, the evidence will be downgraded for indirectness. <u>Intervention:</u> • Population-level interventions (for example, TV and online advertising)
Context	The population of this guideline may overlap with the population of women included in other NICE guidelines (such as postnatal care, antenatal care, intrapartum care, pregnancy and complex social factors or obesity prevention).
Primary outcomes (critical outcomes)	• Changes in folic acid supplementation uptake rate (self-reported or objective measures) Note: if the study reports both self-reported and objective measures, only objective measures will be reported

Secondary outcomes (important outcomes)	• Changes in attitude, confidence and knowledge as part of people's intention to change behaviour
	• Unintended consequences:
	  ○ Increase in inequalities
	  ○ Supplementation wastage

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. Dual sifting will be performed on at least 10% of records; 90% agreement is required. Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. 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

Field	Content
	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 and cohort studies • JBI checklist for prevalence studies • Effective Practice and Organisation of Care (EPOC) RoB Tool for before-and-after studies 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: • Validated scales/continuous outcomes: published MIDs where available

Field	Content
	• 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	Evidence will be stratified by:
	• Folic acid supplementation dose: low-dose (<1 mg daily); medium-dose (≥1 to <5 mg daily); high-dose (≥5 mg daily)
	• BMI thresholds:
	  ○ Overweight range: 25 to 29.99 kg/m^2
	  ○ Obesity range 1: 30 to 34.99 kg/m^2
	  ○ Obesity range 2: 35 to 39.99 kg/m^2
	  ○ Obesity range 3: >40 kg/m^2
	  ○ Follow the NICE guidance on Obesity: identification and classification of overweight and obesity (update) for people with a South Asian, Chinese, other Asian, Middle Eastern, Black African or African-Caribbean family background
	• Age
	  ○ Under 40 years of age
	  ○ Over 40 years of age
	• Deprived socioeconomic group
	• Comorbidities
	
	Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes:
	• Women with disabilities, including learning disabilities and other physical and mental health conditions
	• Women going through assisted conception
	• LGBTQ+ women
	• Geographical variation, for example places without adequate provision of primary care (outside cities).
	• Ethnicity

Field	Content		
	○ White/White British ○ Asian/Asian British ○ Black/African/Caribbean/Black British ○ Mixed/Multiple ethnic groups ○ Other ethnic group Where evidence is stratified or subgrouped 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.		
Type and method of review	☒	Intervention	
	☐	Diagnostic	
	☐	Prognostic	
	☐	Qualitative	
	☐	Epidemiologic	
	☐	Service Delivery	
	☐	Other (please specify)	
Language	English		
Country	England		
Anticipated or actual start date	20/10/2022		
Anticipated completion date	22/11/2023		
Stage of review at time of this submission	Review stage	Started	Completed
	Preliminary searches	☐	☐ x

Field	Content		
	Piloting of the study selection process	☐	☐ x
	Formal screening of search results against eligibility criteria	☐	☐ x
	Data extraction	☐	☐ x
	Risk of bias (quality) assessment	☐	☐ x
	Data analysis	☐	☐ x
Named contact	**5a. Named contact** National Institute for Health and Care Excellence **5b. Named contact e-mail** mandcnutrition@nice.org.uk **5c. Organisational affiliation of the review** National Institute for Health and Care Excellence		
Review team members	From the National Guideline Alliance: • Senior Systematic Reviewer • Systematic Reviewer		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance which receives funding from 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 N'CE'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 mem'er's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		

Field	Content	
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	crd.york.ac.uk/PROSPERO/display_record.php?RecordID=355216	
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • 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 uptake, supplementation, preconception, pre-pregnancy, post-conception	
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; EPOC: Effective Practice and Organisation of Care; EPPI: Evidence for policy and practice information; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; JBI: Joanna Briggs Institute; kg: kilograms; m: metres; mg: milligram; LGBTQ+: lesbian, gay, bisexual, transgender, and queer; MID: minimally important difference; NICE: National Institute for Health and Care Excellence; OECD: Organisation for Economic Co-Operation and Development; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; ROBINS-I: risk of bias in non-randomised studies; SD: standard deviation, TV: television

Appendix B Literature search strategies

Literature search strategies for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

One literature search was performed for the review questions in evidence reviews C and E.

Effectiveness searches

Databases: MEDLINE

Date of last search: 05/12/2023

#	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,kf.
8	or/4-7
9	3 or 8
10	breast feeding/ or lactation/
11	(breastfeed* or breastfed* or breastmilk or (breast adj2 (feed* or fed* or milk*)) or expressed milk* or lactat* or (nursing adj (baby or infant* or mother* or neonate* or newborn*))).ti,ab,kf.
12	10 or 11
13	exp Child/ or exp Infant/ or Minors/ or exp Pediatrics/
14	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or preschool* or schoolchild* or school age? or toddler* or young).ti,ab,kf.
15	(child* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or schoolchild* or school age?).jw,nw.
16	or/13-15
17	3 or 12 or 16
18	exp Folic Acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	18 or 19
21	9 and 20
22	exp Vitamins/ or Dietary Supplements/
23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).ti,ab,kf.
24	(precursor* adj3 vitamin*).ti,ab,kf.
25	((diet* or nutrition*) adj2 supplement*).ti,ab,kf.
26	(calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or 24,25-dihydroxyvitamin D* or ergocalciferol* or ergosterol* or viosterol or vitamin d* or vitamind* or 25 hydroxy* or 25-?OH* or vitamina* or (vitamin adj a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic Acid* or vitaminc or (vitamin adj c)).ti,ab,kf.
27	(vit adj2 (A or C or D)).ti,ab,kf.
28	(healthy start* or healthystart*).ti,ab,kf.
29	or/22-28

#	Searches
30	20 or 29
31	17 and 30
32	Health Knowledge, Attitudes, Practice/ or preconception care/ or prenatal care/ or Health Behavior/
33	Information centers/ or information services/ or information dissemination/
34	Education/ or health education/ or exp consumer health information/ or Health Promotion/
35	(advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*).ti,ab,kf.
36	patient education as topic/ or Correspondence as Topic/ or Posters as Topic/
37	(letter* or correspond* or mail or poster*).ti,ab,kf.
38	exp Communication/
39	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write).ti,ab,kf.
40	exp Mass Media/
41	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*).ti,ab,kf.
42	Informed Consent/
43	(informed adj4 (consent or choice* or decision*)).ti,ab,kf.
44	Reminder Systems/
45	(recall or remind* or prompt* or nudge).ti,ab,kf.
46	(electronic* adj4 invit*).ti,ab,kf.
47	exp internet/ or exp computers, handheld/ or exp Cell Phone/ or mobile applications/ or electronic mail/ or hotlines/
48	((medical or health or electronic or virtual) adj4 (communicat* or educat* or informat* or learn* or coach*)).ti.
49	patient education handout/
50	exp teaching materials/
51	pamphlets/
52	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*).ti.
53	((online or web or internet or digital* or video*) adj3 (based or application* or intervention* or program* or therap*)).ab.
54	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) adj3 (based or application* or intervention* or device* or technolog* or program* or therap*)).ti,ab.
55	(computer* adj4 (handheld or palm top or palmtop or pda or tablet*)).ti.
56	(mobile health or mhealth or m health or ehealth or e health).ti.
57	((mobile health or mhealth or m health or ehealth or e health) adj3 (based or application* or intervention* or program* or therap*)).ab.
58	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?).ti,ab,kf.
59	exp Socioeconomic Factors/
60	health status/ or exp health inequities/
61	((government* or welfare or aid* or social security or relief) adj2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)).ti,ab,kf.
62	Health Services Accessibility/
63	((sexual or health) adj2 (clinic* or center* or centre*)).ti,ab,kf.
64	((preconcept* or pre concept* or prepregnan* or pre pregnan*) adj2 (clinic* or center* or centre* or service? or assessment*)).ti,ab,kf.
65	Community Networks/ or Community-Institutional Relations/
66	((communit* or social) adj4 (network* or relation* or support*)).ti,ab,kf.
67	social support/ or self-help groups/ or Peer Influence/

#	Searches
68	(group* adj2 (support* or self-help*)).ti,ab,kf.
69	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) adj4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)).ti,ab,kf.
70	Mentors/
71	(mentor* or role model*).ti,ab,kf.
72	House Calls/
73	((house or home) adj4 (call* or visit*)).ti,ab,kf.
74	Choice Behavior/ or Decision Making/ or Decision Support Techniques/
75	(decision* adj4 (making or support* or aid*)).ti,ab,kf.
76	risk reduction behavior/ or Motivation/ or "Patient Acceptance of Health Care"/
77	((behavio?r* or lifestyle* or life style*) adj2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)).ti,ab,kf.
78	motivat*.ti,ab,kf.
79	exp psychotherapy/ or exp counseling/ or self care/
80	self care.ti,ab,kf.
81	counsel*.ti,ab,kf.
82	((diet* or nutrient* or nutrition* or lifestyle*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
83	((behavio?r* or cogniti* or psycho*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
84	or/32-83
85	"treatment adherence and compliance"/ or patient compliance/ or medication adherence/ or Guideline Adherence/
86	(uptake* or up-tak* or takeup* or tak*-up* or aware* or adher* or nonadher* or non adher* or comply* or complies or complian* or adopt* or implement).ti,ab,kf.
87	(supplement* adj3 behav*).ti,ab,kf.
88	or/85-87
89	84 and 88
90	21 and 89
91	31 and 89
92	letter/
93	editorial/
94	news/
95	exp historical article/
96	Anecdotes as Topic/
97	comment/
98	case report/
99	(letter or comment*).ti.
100	or/92-99
101	randomized controlled trial/ or random*.ti,ab.
102	100 not 101
103	animals/ not humans/
104	exp Animals, Laboratory/
105	exp Animal Experimentation/
106	exp Models, Animal/
107	exp Rodentia/
108	(rat or rats or mouse or mice or rodent*).ti.
109	or/102-108
110	90 not 109

#	Searches
111	limit 110 to English language
112	91 not 109
113	limit 112 to English language
114	randomized controlled trial.pt.
115	controlled clinical trial.pt.
116	pragmatic clinical trial.pt.
117	randomi#ed.ab.
118	placebo.ab.
119	drug therapy.fs.
120	randomly.ab.
121	trial.ab.
122	groups.ab.
123	or/114-122
124	Clinical Trials as topic.sh.
125	trial.ti.
126	or/114-118,120,124-125
127	Meta-Analysis/
128	Meta-Analysis as Topic/
129	(meta analy* or metanaly* or metaanaly*).ti,ab.
130	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
131	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
132	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
133	(search* adj4 literature).ab.
134	(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.
135	cochrane.jw.
136	or/127-135
137	111 and (126 or 136)
138	113 and (126 or 136)
139	Observational Studies as Topic/
140	Observational Study/
141	Epidemiologic Studies/
142	exp Case-Control Studies/
143	exp Cohort Studies/
144	Cross-Sectional Studies/
145	Controlled Before-After Studies/
146	Historically Controlled Study/
147	Interrupted Time Series Analysis/
148	Comparative Study.pt.
149	case control$.tw.
150	case series.tw.
151	(cohort adj (study or studies)).tw.
152	cohort analy$.tw.
153	(follow up adj (study or studies)).tw.
154	(observational adj (study or studies)).tw.
155	longitudinal.tw.
156	prospective.tw.
157	retrospective.tw.
158	cross sectional.tw.
159	or/139-158

#	Searches
160	111 and 159
161	160 not 137
162	113 and 159
163	162 not 138
164	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/
165	"organisation for economic co-operation and development"/
166	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 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/
167	european union/
168	developed countries/
169	or/165-168
170	164 not 169
171	137 not 170
172	138 not 170
173	161 not 170
174	163 not 170

Databases: Embase

Date of last search:05/12/2023

#	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,kf.
8	or/4-7
9	3 or 8
10	exp breast feeding/ or lactation/
11	(breastfeed* or breastfed* or breastmilk or (breast adj2 (feed* or fed* or milk*)) or expressed milk* or lactat* or (nursing adj (baby or infant* or mother* or neonate* or newborn*))).ti,ab,kf.

#	Searches
12	10 or 11
13	exp child/ or "minor (person)"/ or exp pediatrics/
14	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or preschool* or schoolchild* or school age? or toddler* or young).ti,ab,kf.
15	(child* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or schoolchild* or school age?).jx.
16	or/13-15
17	3 or 12 or 16
18	folic acid/
19	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,kf.
20	18 or 19
21	9 and 20
22	exp vitamin/ or dietary supplement/
23	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).ti,ab,kf.
24	(precursor* adj3 vitamin*).ti,ab,kf.
25	((diet* or nutrition*) adj2 supplement*).ti,ab,kf.
26	(calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or 24,25-dihydroxyvitamin D* or ergocalciferol* or ergosterol* or viosterol or vitamin d* or vitamind* or 25 hydroxy* or 25-?OH* or vitamina* or (vitamin adj a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic Acid* or vitaminc or (vitamin adj c)).ti,ab,kf.
27	(vit adj2 (A or C or D)).ti,ab,kf.
28	(healthy start* or healthystart*).ti,ab,kf.
29	or/22-28
30	20 or 29
31	17 and 30
32	attitude to health/ or prepregnancy care/ or prenatal care/ or health behavior/
33	information center/ or information service/ or information dissemination/
34	(advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*).ti,ab,kf.
35	patient education/ or writing/ or publication/
36	(letter* or correspond* or mail or poster*).ti,ab,kf.
37	exp interpersonal communication/
38	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write).ti,ab,kf.
39	mass medium/
40	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*).ti,ab,kf.
41	informed consent/
42	(informed adj4 (consent or choice* or decision*)).ti,ab,kf.
43	reminder system/
44	(recall or remind* or prompt* or nudge).ti,ab,kf.
45	(electronic* adj4 invit*).ti,ab,kf.
46	exp internet/ or personal digital assistant/ or exp mobile phone/ or exp mobile application/ or e-mail/ or hotline/
47	((medical or health or electronic or virtual) adj4 (communicat* or educat* or informat* or learn* or coach*)).ti.
48	exp teaching/
49	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*).ti.

#	Searches
50	((online or web or internet or digital* or video*) adj3 (based or application* or intervention* or program* or therap*)).ab.
51	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) adj3 (based or application* or intervention* or device* or technolog* or program* or therap*)).ti,ab.
52	(computer* adj4 (handheld or palm top or palmtop or pda or tablet*)).ti.
53	(mobile health or mhealth or m health or ehealth or e health).ti.
54	((mobile health or mhealth or m health or ehealth or e health) adj3 (based or application* or intervention* or program* or therap*)).ab.
55	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?).ti,ab,kf.
56	exp socioeconomics/
57	health status/ or health disparity/
58	((government* or welfare or aid* or social security or relief) adj2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)).ti,ab,kf.
59	health care access/
60	((sexual or health) adj2 (clinic* or center* or centre*)).ti,ab,kf.
61	((preconcept* or pre concept* or prepregnan* or pre pregnan*) adj2 (clinic* or center* or centre* or service? or assessment*)).ti,ab,kf.
62	community care/ or public relations/
63	((communit* or social) adj4 (network* or relation* or support*)).ti,ab,kf.
64	social support/ or self help/ or peer pressure/
65	(group* adj2 (support* or self-help*)).ti,ab,kf.
66	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) adj4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)).ti,ab,kf.
67	mentor/
68	(mentor* or role model*).ti,ab,kf.
69	home visit/
70	((house or home) adj4 (call* or visit*)).ti,ab,kf.
71	decision making/ or decision support system/
72	(decision* adj4 (making or support* or aid*)).ti,ab,kf.
73	risk reduction/ or motivation/ or patient attitude/
74	((behavio?r* or lifestyle* or life style*) adj2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)).ti,ab,kf.
75	motivat*.ti,ab,kf.
76	exp psychotherapy/ or exp counseling/ or self care/
77	self care.ti,ab,kf.
78	counsel*.ti,ab,kf.
79	((diet* or nutrient* or nutrition* or lifestyle*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
80	((behavio?r* or cogniti* or psycho*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
81	or/32-80
82	exp patient compliance/ or protocol compliance/
83	(uptake* or up-tak* or takeup* or tak*-up* or aware* or adher* or nonadher* or non adher* or comply* or complies or complian* or adopt* or implement).ti,ab,kf.
84	(supplement* adj3 behav*).ti,ab,kf.
85	or/82-84
86	81 and 85
87	21 and 86
88	31 and 86
89	letter.pt. or letter/

#	Searches
90	note.pt.
91	editorial.pt.
92	case report/ or case study/
93	(letter or comment*).ti.
94	or/89-93
95	randomized controlled trial/ or random*.ti,ab.
96	94 not 95
97	animal/ not human/
98	nonhuman/
99	exp Animal Experiment/
100	exp Experimental Animal/
101	animal model/
102	exp Rodent/
103	(rat or rats or mouse or mice or rodent*).ti.
104	or/96-103
105	87 not 104
106	limit 105 to English language
107	88 not 104
108	limit 107 to English language
109	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
110	106 not 109
111	108 not 109
112	random*.ti,ab.
113	factorial*.ti,ab.
114	(crossover* or cross over*).ti,ab.
115	((doubl* or singl*) adj blind*).ti,ab.
116	(assign* or allocat* or volunteer* or placebo*).ti,ab.
117	crossover procedure/
118	single blind procedure/
119	randomized controlled trial/
120	double blind procedure/
121	or/112-120
122	systematic review/
123	meta-analysis/
124	(meta analy* or metanaly* or metaanaly*).ti,ab.
125	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
126	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
127	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
128	(search* adj4 literature).ab.
129	(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.
130	((pool* or combined) adj2 (data or trials or studies or results)).ab.
131	cochrane.jw.
132	or/122-131
133	110 and (121 or 132)
134	111 and (121 or 132)
135	Clinical study/
136	Case control study/
137	Family study/
138	Longitudinal study/

#	Searches
139	Retrospective study/
140	comparative study/
141	Prospective study/
142	Randomized controlled trials/
143	141 not 142
144	Cohort analysis/
145	cohort analy$.tw.
146	(Cohort adj (study or studies)).tw.
147	(Case control$ adj (study or studies)).tw.
148	(follow up adj (study or studies)).tw.
149	(observational adj (study or studies)).tw.
150	(epidemiologic$ adj (study or studies)).tw.
151	(cross sectional adj (study or studies)).tw.
152	case series.tw.
153	prospective.tw.
154	retrospective.tw.
155	or/135-140,143-154
156	110 and 155
157	156 not 133
158	111 and 155
159	158 not 134
160	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 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/
161	exp "organisation for economic co-operation and development"/
162	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/
163	european union/
164	developed country/
165	or/161-164
166	160 not 165
167	133 not 166
168	134 not 166
169	157 not 166
170	159 not 166

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

Date of last search: 07/12/2023

#	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: [Breast Feeding] this term only
#13	MeSH descriptor: [Lactation] this term only
#14	(breastfeed* or breastfed* or breastmilk or (breast NEAR/2 (feed* or fed* or milk*)) or expressed NEXT milk* or lactat* or (nursing NEAR (baby or infant* or mother* or neonate* or newborn*))):ti,ab,kw
#15	{OR #12-#14}
#16	MeSH descriptor: [Child] explode all trees
#17	MeSH descriptor: [Infant] explode all trees
#18	MeSH descriptor: [Minors] this term only
#19	MeSH descriptor: [Pediatrics] explode all trees
#20	(child* or baby or babies or boy or boys or girl or girls or infan* or juvenile or juveniles or kid or kids or kindergar* or minors or neonat* or newborn or newborns or pediatric* or paediatric* or preschool* or schoolchild* or "school age" or "school aged" or toddler* or young):ti,ab,kw
#21	(child* or baby or babies or infan* or juvenile or juveniles or kindergar* or neonat* or newborn or newborns or pediatric* or paediatric* or schoolchild* or "school age" or "school aged"):so
#22	{OR #16-#21}
#23	#5 OR #15 OR #22
#24	MeSH descriptor: [Folic Acid] explode all trees
#25	(folic NEXT acid* or folate* or folacin or "vitamin b9" or "vitamin b 9" or "vitamin m" or pteroylglutamic NEXT acid* or folvite):ti,ab,kw
#26	#24 OR #25
#27	#11 AND #26
#28	MeSH descriptor: [Vitamins] explode all trees
#29	MeSH descriptor: [Dietary Supplements] this term only
#30	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* NEXT micronutrient*):ti,ab,kw
#31	(precursor* NEAR/3 vitamin*):ti,ab,kw
#32	((diet* or nutrition*) NEAR/2 supplement*):ti,ab,kw
#33	(calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or "24,25 dihydroxyvitamin D" or ergocalciferol* or ergosterol* or viosterol or "vitamin d" or vitamind or 25 NEXT hydroxy* or 25 NEXT OH* or vitamina* or (vitamin NEAR a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta NEXT carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic NEXT Acid* or vitaminc or (vitamin NEAR c)):ti,ab,kw
#34	(vit NEAR/2 (A or C or D)):ti,ab,kw
#35	(healthy NEXT start* or healthystart*):ti,ab,kw
#36	{OR #28-#35}

#	Searches
#37	#26 OR #36
#38	#23 AND #37
#39	MeSH descriptor: [Health Knowledge, Attitudes, Practice] this term only
#40	MeSH descriptor: [Preconception Care] this term only
#41	MeSH descriptor: [Prenatal Care] this term only
#42	MeSH descriptor: [Health Behavior] this term only
#43	MeSH descriptor: [Information Centers] this term only
#44	MeSH descriptor: [Information Services] this term only
#45	MeSH descriptor: [Information Dissemination] this term only
#46	MeSH descriptor: [Education] this term only
#47	MeSH descriptor: [Health Education] this term only
#48	MeSH descriptor: [Consumer Health Information] explode all trees
#49	MeSH descriptor: [Health Promotion] this term only
#50	(advice* or advise* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*):ti,ab,kw
#51	MeSH descriptor: [Patient Education as Topic] this term only
#52	MeSH descriptor: [Correspondence as Topic] this term only
#53	MeSH descriptor: [Posters as Topic] this term only
#54	(letter* or correspond* or mail or poster*):ti,ab,kw
#55	MeSH descriptor: [Communication] explode all trees
#56	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write):ti,ab,kw
#57	MeSH descriptor: [Mass Media] this term only
#58	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*):ti,ab,kw
#59	MeSH descriptor: [Informed Consent] this term only
#60	(informed NEAR/4 (consent or choice* or decision*)):ti,ab,kw
#61	MeSH descriptor: [Reminder Systems] this term only
#62	(recall or remind* or prompt* or nudge):ti,ab,kw
#63	(electronic* NEAR/4 invit*):ti,ab,kw
#64	MeSH descriptor: [Internet] explode all trees
#65	MeSH descriptor: [Computers, Handheld] explode all trees
#66	MeSH descriptor: [Cell Phone] this term only
#67	MeSH descriptor: [Mobile Applications] this term only
#68	MeSH descriptor: [Electronic Mail] this term only
#69	MeSH descriptor: [Hotlines] this term only
#70	((medical or health or electronic or virtual) NEAR/4 (communicat* or educat* or informat* or learn* or coach*)):ti
#71	MeSH descriptor: [Patient Education Handout] this term only
#72	MeSH descriptor: [Teaching Materials] this term only
#73	MeSH descriptor: [Pamphlets] this term only
#74	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e NEXT learn* or email* or e NEXT mail* or electronic NEXT mail* or facebook or "face book" or facetime or "face time" or factsheet* or forum* or flyer or guidebook* or handout* or hand NEXT out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile NEXT phone* or multimedia NEXT messag* or newsletter* or pamphlet* or palm NEXT pilot* or personal NEXT digital NEXT assistant* or phone* or pocket NEXT pc* or podcast* or postcard* or poster or posters or skype* or smartphone* or smart NEXT phone* or smartwatch* or smart NEXT watch* or "social media" or social NEXT network* or sms or telephone* or text NEXT messag* or twitter or tweet* or video* or web* or wiki* or youtube*):ti
#75	((online or web or internet or digital* or video*) NEAR/3 (based or application* or intervention* or program* or therap*)):ab
#76	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) NEAR/3 (based or application* or intervention* or device* or technolog* or program* or therap*)):ti,ab
#77	(computer* NEAR/4 (handheld or "palm top" or palmtop or pda or tablet*)):ti

#	Searches
#78	("mobile health" or mhealth or "m health" or ehealth or "e health"):ti
#79	(("mobile health" or mhealth or "m health" or ehealth or "e health") NEAR/3 (based or application* or intervention* or program* or therap*)):ab
#80	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar or bars):ti,ab,kw
#81	MeSH descriptor: [Socioeconomic Factors] explode all trees
#82	MeSH descriptor: [Health Status] this term only
#83	MeSH descriptor: [Health Inequities] explode all trees
#84	((government* or welfare or aid* or "social security" or relief) NEAR/2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)):ti,ab,kw
#85	MeSH descriptor: [Health Services Accessibility] this term only
#86	((sexual or health) NEAR/2 (clinic* or center* or centre*)):ti,ab,kw
#87	((preconcept* or pre NEXT concept* or prepregnan* or pre NEXT pregnan*) NEAR/2 (clinic* or center* or centre* or service or services or assessment*)):ti,ab,kw
#88	MeSH descriptor: [Community Networks] this term only
#89	MeSH descriptor: [Community-Institutional Relations] this term only
#90	((communit* or social) NEAR/4 (network* or relation* or support*)):ti,ab,kw
#91	MeSH descriptor: [Social Support] this term only
#92	MeSH descriptor: [Self-Help Groups] this term only
#93	MeSH descriptor: [Peer Influence] this term only
#94	(group* NEAR/2 (support* or self NEXT help*)):ti,ab,kw
#95	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health NEXT visitor* or midwife or midwives or social NEXT worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health NEXT professional* or clinician* or consultant* or primary NEXT care* or dietician* or nutritionist* or HCP*1) NEAR/4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)):ti,ab,kw
#96	MeSH descriptor: [Mentors] this term only
#97	(mentor* or role NEXT model*):ti,ab,kw
#98	MeSH descriptor: [House Calls] this term only
#99	((house or home) NEAR/4 (call* or visit*)):ti,ab,kw
#100	MeSH descriptor: [Choice Behavior] this term only
#101	MeSH descriptor: [Decision Making] this term only
#102	MeSH descriptor: [Decision Support Techniques] this term only
#103	(decision* NEAR/4 (making or support* or aid*)):ti,ab,kw
#104	MeSH descriptor: [Risk Reduction Behavior] this term only
#105	MeSH descriptor: [Motivation] this term only
#106	MeSH descriptor: [Patient Acceptance of Health Care] this term only
#107	((behavior* or behaviour* or lifestyle* or life NEXT style*) NEAR/2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)):ti,ab,kw
#108	motivat*:ti,ab,kw
#109	MeSH descriptor: [Psychotherapy] explode all trees
#110	MeSH descriptor: [Counseling] explode all trees
#111	MeSH descriptor: [Self Care] this term only
#112	self care:ti,ab,kw
#113	counsel*:ti,ab,kw
#114	((diet* or nutrient* or nutrition* or lifestyle*) NEAR/2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)):ti,ab,kw
#115	((behavior* or behaviour* or cogniti* or psycho*) NEAR/2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)):ti,ab,kw
#116	{OR #39-#115}
#117	MeSH descriptor: [Treatment Adherence and Compliance] this term only
#118	MeSH descriptor: [Patient Compliance] this term only

#	Searches
#119	MeSH descriptor: [Medication Adherence] this term only
#120	MeSH descriptor: [Guideline Adherence] this term only
#121	(uptake* or up NEXT tak* or takeup* or tak* NEXT up* or aware* or adher* or nonadher* or non NEXT adher* or comply* or complies or complian* or adopt* or implement):ti,ab,kw
#122	(supplement* NEAR/3 behav*):ti,ab,kw
#123	{OR #117-#122}
#124	#116 AND #123
#125	#27 AND #124
#126	#38 AND #124
#127	conference:pt or (clinicaltrials or trialsearch):so
#128	#125 NOT #127
#129	#126 NOT #127

Database: PsycINFO

Date of last search: 05/12/2023

#	Searches
1	exp Pregnancy/ or Prenatal Care/ or Perinatal Period/
2	(antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*).ti,ab,id.
3	1 or 2
4	(periconcept* or peri concept* or preconcept* or pre concept* or prepregnan* or pre pregnan*).ti,ab,id.
5	((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,id.
6	(start* adj2 family).ti,ab,id.
7	or/4-6
8	3 or 7
9	breast feeding/ or lactation/
10	(breastfeed* or breastfed* or breastmilk or (breast adj2 (feed* or fed* or milk*)) or expressed milk* or lactat* or (nursing adj (baby or infant* or mother* or neonate* or newborn*))).ti,ab,id.
11	9 or 10
12	(child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or preschool* or schoolchild* or school age? or toddler* or young).ti,ab,id.
13	(child* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or schoolchild* or school age?).jn,jx.
14	12 or 13
15	3 or 11 or 14
16	exp Folic Acid/
17	(folic acid* or folate* or folacin or vitamin b9 or vitamin b 9 or vitamin m or pteroylglutamic acid* or folvite).ti,ab,id.
18	16 or 17
19	8 and 18
20	exp Vitamins/ or Dietary Supplements/
21	(vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*).ti,ab,id.
22	(precursor* adj3 vitamin*).ti,ab,id.
23	((diet* or nutrition*) adj2 supplement*).ti,ab,id.
24	(calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or 24,25-dihydroxyvitamin D* or ergocalciferol* or ergosterol* or viosterol or vitamin d* or vitamind* or 25 hydroxy* or 25-?OH* or vitamina* or (vitamin adj a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic Acid* or vitaminc or (vitamin adj c)).ti,ab,id.
25	(vit adj2 (A or C or D)).ti,ab,id.
26	(healthy start* or healthystart*).ti,ab,id.

#	Searches
27	or/20-26
28	19 or 27
29	15 and 28
30	Health Attitudes/ or Health Knowledge/ or health behavior/ or Prenatal Care/
31	information/ or information dissemination/ or information services/
32	Education/ or Health Education/ or exp health information/ or Health Promotion/
33	(advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*).ti,ab,id.
34	Client Education/ or knowledge transfer/
35	(letter* or correspond* or mail or poster*).ti,ab,id.
36	exp Communication/
37	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write).ti,ab,id.
38	exp Mass Media/
39	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*).ti,ab,id.
40	Informed Consent/
41	(informed adj4 (consent or choice* or decision*)).ti,ab,id.
42	(recall or remind* or prompt* or nudge).ti,ab,id.
43	(electronic* adj4 invit*).ti,ab,id.
44	exp Internet/ or exp mobile devices/ or mobile applications/ or computer mediated communication/ or Hot Line Services/
45	((medical or health or electronic or virtual) adj4 (communicat* or educat* or informat* or learn* or coach*)).ti.
46	teaching/
47	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*).ti.
48	((online or web or internet or digital* or video*) adj3 (based or application* or intervention* or program* or therap*)).ab.
49	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) adj3 (based or application* or intervention* or device* or technolog* or program* or therap*)).ti,ab.
50	(computer* adj4 (handheld or palm top or palmtop or pda or tablet*)).ti.
51	(mobile health or mhealth or m health or ehealth or e health).ti.
52	((mobile health or mhealth or m health or ehealth or e health) adj3 (based or application* or intervention* or program* or therap*)).ab.
53	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?).ti,ab,id.
54	exp Socioeconomic Factors/
55	Health Status/ or health disparities/
56	((government* or welfare or aid* or social security or relief) adj2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)).ti,ab,id.
57	health care access/
58	((sexual or health) adj2 (clinic* or center* or centre*)).ti,ab,id.
59	((preconcept* or pre concept* or prepregnan* or pre pregnan*) adj2 (clinic* or center* or centre* or service? or assessment*)).ti,ab,id.
60	Social Networks/
61	((communit* or social) adj4 (network* or relation* or support*)).ti,ab,id.
62	Social Support/ or support groups/ or exp interpersonal influences/
63	(group* adj2 (support* or self-help*)).ti,ab,id.
64	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or

#	Searches
	dietician* or nutritionist* or HCP*1) adj4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)).ti,ab,id.
65	Mentor/
66	(mentor* or role model*).ti,ab,id.
67	Home Visiting Programs/
68	((house or home) adj4 (call* or visit*)).ti,ab,id.
69	Choice Behavior/ or Decision Making/ or Decision Support Systems/
70	(decision* adj4 (making or support* or aid*)).ti,ab,id.
71	preventive health behavior/ or Motivation/
72	((behavio?r* or lifestyle* or life style*) adj2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)).ti,ab,id.
73	motivat*.ti,ab,id.
74	exp Psychotherapy/ or exp Counseling/ or Self-Care/
75	self care.ti,ab,id.
76	counsel*.ti,ab,id.
77	((diet* or nutrient* or nutrition* or lifestyle*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,id.
78	((behavio?r* or cogniti* or psycho*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,id.
79	or/30-78
80	treatment compliance/
81	(uptake* or up-tak* or takeup* or tak*-up* or aware* or adher* or nonadher* or non adher* or comply* or complies or complian* or adopt* or implement).ti,ab,id.
82	(supplement* adj3 behav*).ti,ab,id.
83	or/80-82
84	79 and 83
85	19 and 84
86	29 and 84
87	(letter or editorial or comment reply).dt. or case report/
88	(letter or comment*).ti.
89	or/87-88
90	exp randomized controlled trial/
91	random*.ti,ab.
92	or/90-91
93	89 not 92
94	animal.po.
95	(rat or rats or mouse or mice or rodent*).ti.
96	or/93-95
97	85 not 96
98	86 not 96
99	limit 97 to English language
100	limit 98 to English language
101	clinical trial.md.
102	Clinical trials/
103	Randomized controlled trials/
104	Randomized clinical trials/
105	assign*.ti,ab.
106	allocat*.ti,ab.
107	crossover*.ti,ab.
108	cross over*.ti,ab.
109	((doubl* or singl*) adj blind*).ti,ab.

#	Searches
110	factorial*.ti,ab.
111	placebo*.ti,ab.
112	random*.ti,ab.
113	volunteer*.ti,ab.
114	trial?.ti,ab.
115	or/101-114
116	(meta analysis or "systematic review").md.
117	META ANALYSIS/
118	SYSTEMATIC REVIEW/
119	(meta analy* or metanaly* or metaanaly*).ti,ab.
120	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
121	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
122	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
123	(search* adj4 literature).ab.
124	cochrane.jw.
125	((pool* or combined) adj2 (data or trials or studies or results)).ab.
126	(medline or pubmed or cochrane or embase or psychlit or psyclit or cinahl or science citation index or bids or cancerlit).ab.
127	or/116-126
128	99 and (115 or 127)
129	100 and (115 or 127)
130	FOLLOWUP STUDY/
131	(follow up adj (study or studies)).tw.
132	(observational adj (study or studies)).tw.
133	(epidemiologic$ adj (study or studies)).tw.
134	(cross sectional adj (study or studies)).tw.
135	(Case control$ adj (study or studies)).tw.
136	TREATMENT OUTCOMES/
137	treatment outcome.md.
138	CLINICAL TRIALS/
139	clinical trial.md.
140	chang$.tw.
141	evaluat$.tw.
142	reviewed.tw.
143	prospective$.tw.
144	retrospective$.tw.
145	baseline.tw.
146	cohort.tw.
147	case series.tw.
148	(compare$ or compara$).tw.
149	or/130-148
150	99 and 149
151	150 not 128
152	100 and 149
153	152 not 129

Database: CINAHL

Date of last search: 05/12/2023

#	Searches
S123	S40 AND S121 (English language, Human)
S122	S29 AND S121 (English language, Human)
S121	S114 AND S120
S120	S115 OR S116 OR S117 OR S118 OR S119
S119	TI (supplement* N3 behav*) OR AB (supplement* N3 behav*)
S118	TI ((uptake* or up-tak* or takeup* or tak*-up* or aware* or adher* or nonadher* or non adher* or comply* or complies or complian* or adopt* or implement)) OR AB ((uptake* or up-tak* or takeup* or tak*-up* or aware* or adher* or nonadher* or non adher* or comply* or complies or complian* or adopt* or implement))
S117	(MH "Guideline Adherence")
S116	(MH "Patient Compliance")
S115	(MH "Medication Compliance")
S114	S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 OR S103 OR S104 OR S105 OR S106 OR S107 OR S108 OR S109 OR S110 OR S111 OR S112 OR S113
S113	TI (((behavio?r* or cogniti* or psycho*) N2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*))) OR AB (((behavio?r* or cogniti* or psycho*) N2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)))
S112	TI (((diet* or nutrient* or nutrition* or lifestyle*) N2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*))) OR AB (((diet* or nutrient* or nutrition* or lifestyle*) N2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)))
S111	TI counsel* OR AB counsel*
S110	TI self care OR AB self care
S109	(MH "Self Care")
S108	(MH "Counseling+")
S107	(MH "Psychotherapy+")
S106	TI motivat* OR AB motivat*
S105	TI (((behavio?r* or lifestyle* or life style*) N2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*))) OR AB (((behavio?r* or lifestyle* or life style*) N2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)))
S104	(MH "Motivation")
S103	TI ((decision* N4 (making or support* or aid*))) OR AB ((decision* N4 (making or support* or aid*)))
S102	(MH "Decision Making") OR (MH "Decision Making, Patient") OR (MH "Decision Support Techniques")
S101	TI (((house or home) N4 (call* or visit*))) OR AB (((house or home) N4 (call* or visit*)))
S100	(MH "Home Visits")
S99	TI ((mentor* or role model*)) OR AB ((mentor* or role model*))
S98	(MH "Mentorship")
S97	TI (((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) N4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*))) OR AB (((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) N4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)))
S96	TI ((group* N2 (support* or self-help*))) OR AB ((group* N2 (support* or self-help*)))
S95	(MH "Peer Pressure")

#	Searches
S94	(MH "Support Groups")
S93	(MH "Support, Social+")
S92	TI (((communit* or social) N4 (network* or relation* or support*))) OR AB (((communit* or social) N4 (network* or relation* or support*)))
S91	(MH "Community-Institutional Relations")
S90	(MH "Community Networks")
S89	TI (((preconcept* or pre concept* or prepregnan* or pre pregnan*) N2 (clinic* or center* or centre* or service? or assessment*)).) OR AB (((preconcept* or pre concept* or prepregnan* or pre pregnan*) N2 (clinic* or center* or centre* or service? or assessment*)).)
S88	TI (((sexual or health) N2 (clinic* or center* or centre*))) OR AB (((sexual or health) N2 (clinic* or center* or centre*)))
S87	(MH "Health Services Accessibility")
S86	TI (((government* or welfare or aid* or social security or relief) N2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*))) OR AB (((government* or welfare or aid* or social security or relief) N2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)))
S85	(MH "Health Inequities")
S84	(MH "Health Status")
S83	(MH "Socioeconomic Factors+")
S82	TI ((cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?)) OR AB ((cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?))
S81	AB ((mobile health or mhealth or m health or ehealth or e health) N3 (based or application* or intervention* or program* or therap*))
S80	TI (mobile health or mhealth or m health or ehealth or e health)
S79	TI (computer* N4 (handheld or palm top or palmtop or pda or tablet*))
S78	TI (((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) N3 (based or application* or intervention* or device* or technolog* or program* or therap*))) OR AB (((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) N3 (based or application* or intervention* or device* or technolog* or program* or therap*)))
S77	AB ((online or web or internet or digital* or video*) N3 (based or application* or intervention* or program* or therap*))
S76	TI (app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*)
S75	(MH "Pamphlets")
S74	(MH "Teaching Materials+")
S73	TI (((medical or health or electronic or virtual) N4 (communicat* or educat* or informat* or learn* or coach*)))
S72	(MH "Telephone Information Services")
S71	(MH "Email")
S70	(MH "Mobile Applications")
S69	(MH "Cellular Phone+")
S68	(MH "Computers, Hand-Held+")
S67	(MH "Internet+")
S66	TI (electronic* N4 invit*) OR AB (electronic* N4 invit*)
S65	TI ((recall or remind* or prompt* or nudge)) OR AB ((recall or remind* or prompt* or nudge))
S64	(MH "Reminder Systems")
S63	TI ((informed N4 (consent or choice* or decision*))) OR AB ((informed N4 (consent or choice* or decision*)))
S62	(MH "Consent")
S61	TI ((media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*)) OR AB ((media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*))
S60	(MH "Communications Media+")

#	Searches
S59	TI ((communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write)) OR AB ((communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write))
S58	(MH "Communication+")
S57	TI ((letter* or correspond* or mail or poster*)) OR AB ((letter* or correspond* or mail or poster*))
S56	(MH "Posters")
S55	(MH "Writing+")
S54	(MH "Patient Education")
S53	TI ((advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*)) OR AB ((advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*))
S52	(MH "Health Promotion")
S51	(MH "Consumer Health Information+")
S50	(MH "Health Education")
S49	(MH "Education")
S48	(MH "Selective Dissemination of Information")
S47	(MH "Information Services")
S46	(MH "Information Centers")
S45	(MH "Health Behavior")
S44	(MH "Prenatal Care")
S43	(MH "Prepregnancy Care")
S42	(MH "Attitude to Health")
S41	(MH "Health Knowledge")
S40	S25 AND S39
S39	S28 OR S38
S38	S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S37	TI ((healthy start* or healthystart*)) OR AB ((healthy start* or healthystart*))
S36	TI ((vit N2 (A or C or D))) OR AB ((vit N2 (A or C or D)))
S35	TI ((calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or 24,25-dihydroxyvitamin D* or ergocalciferol* or ergosterol* or viosterol or vitamin d* or vitamind* or 25 hydroxy* or 25-?OH* or vitamina* or (vitamin N1 a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic Acid* or vitaminc or (vitamin N1 c))) OR AB ((calciferol* or calcifediol* or calciol* or cholecalciferol* or hydroxycholecalciferol* or dihydroxycholecalciferol* or dihydrotachysterol* or calcitriol* or 24,25-dihydroxyvitamin D* or ergocalciferol* or ergosterol* or viosterol or vitamin d* or vitamind* or 25 hydroxy* or 25-?OH* or vitamina* or (vitamin N1 a) or retinol* or retinoid* or retinyl* or retinaldehyde* or carotenoid* or beta carotene* or betacarotene* or tocopherol* or ascorb* or Dehydroascorbic Acid* or vitaminc or (vitamin N1 c)))
S34	TI (((diet* or nutrition*) N2 supplement*)) OR AB (((diet* or nutrition*) N2 supplement*))
S33	TI (precursor* N3 vitamin*) OR AB (precursor* N3 vitamin*)
S32	TI ((vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*)) OR AB ((vitamin* or previtamin* or provitamin* or multivitamin* or micronutrient* or multimicronutrient* or multi* micronutrient*))
S31	(MH "Dietary Supplements")
S30	(MH "Vitamins+")
S29	S11 AND S28
S28	S26 OR S27
S27	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))
S26	(MH "Folic Acid+")
S25	S5 OR S17 OR S24
S24	S18 OR S19 OR S20 OR S21 OR S22 OR S23
S23	TI ((child* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or schoolchild* or school age?)) OR AB ((child* or baby or babies or infan* or juvenile? or kindergar* or neonat* or newborn? or p?ediatric* or schoolchild* or school age?))

#	Searches
S22	TI ((child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or preschool* or schoolchild* or school age? or toddler* or young)) OR AB ((child* or baby or babies or boy? or girl? or infan* or juvenile? or kid? or kindergar* or minors or neonat* or newborn? or p?ediatric* or preschool* or schoolchild* or school age? or toddler* or young))
S21	(MH "Pediatrics+")
S20	(MH "Minors (Legal)")
S19	(MH "Infant+")
S18	(MH "Child+")
S17	S12 OR S13 OR S14 OR S15 OR S16
S16	TI ((nursing N1 (baby or infant* or mother* or neonate* or newborn*))) OR AB ((nursing N1 (baby or infant* or mother* or neonate* or newborn*)))
S15	TI ((breastfeed* or breastfed* or breastmilk or expressed milk* or lactat*)) OR AB ((breastfeed* or breastfed* or breastmilk or expressed milk* or lactat*))
S14	TI ((breast N2 (feed* or fed* or milk*))) OR AB ((breast N2 (feed* or fed* or milk*)))
S13	(MH "Lactation")
S12	(MH "Breast Feeding+")
S11	S5 OR S10
S10	S6 OR S7 OR S8 OR S9
S9	TI (start* N2 family) OR AB (start* N2 family)
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*)))
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*))
S6	(MH "Prepregnancy Care")
S5	S1 OR S2 OR S3 OR S4
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*))
S3	(MH "Prenatal Care")
S2	(MH "Expectant Mothers")
S1	(MH "Pregnancy+")

Database: EPISTEMONIKOS

Date of last search: 05/12/2023

#	Searches
1	((advanced_title_en:((pregnan* OR antenatal OR prenatal OR periconcept* OR preconcept* OR prepregnan*)) OR advanced_abstract_en:((pregnan* OR antenatal OR prenatal OR periconcept* OR preconcept* OR prepregnan*))
2	(advanced_title_en:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite)) OR advanced_abstract_en:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite))
3	1 AND 2
4	((advanced_title_en:((uptake* OR up-tak* OR takeup* OR tak*-up* OR aware* OR adher* OR nonadher* OR non-adher* OR comply* OR complies OR complian* OR adopt* OR implement)) OR advanced_abstract_en:((uptake* OR up-tak* OR takeup* OR tak*-up* OR aware* OR adher* OR nonadher* OR non-adher* OR comply* OR complies OR complian* OR adopt* OR implement))
5	3 AND 4
6	((advanced_title_en:((pregnan* OR breastfeeding OR breastfed OR lactat* OR child* OR infant* OR baby OR babies OR newborn)) OR advanced_abstract_en:((pregnan* OR breastfeeding OR breastfed OR lactat* OR child* OR infant* OR baby OR babies OR newborn))
7	((advanced_title_en:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite)) OR advanced_abstract_en:((folic acid* OR folate* OR folacin OR vitamin b9 OR pteroylglutamic acid* OR folvite))
8	(advanced_title_en:((vitamin* OR previtamin* OR provitamin* OR multivitamin* OR "healthy start" OR healthystart)) OR advanced_abstract_en:((vitamin* OR previtamin* OR provitamin* OR multivitamin* OR "healthy start" OR healthystart))))

#	Searches
9	7 OR 8
10	6 AND 9
11	((advanced_title_en:((uptake* OR up-tak* OR takeup* OR tak*-up* OR aware* OR adher* OR nonadher* OR non-adher* OR comply* OR complies OR complian* OR adopt* OR implement)) OR advanced_abstract_en:((uptake* OR up-tak* OR takeup* OR tak*-up* OR aware* OR adher* OR nonadher* OR non-adher* OR comply* OR complies OR complian* OR adopt* OR implement))
12	10 AND 11
13	5 OR 12
	[Filters: protocol=no, classification=systematic-review, cochrane=missing]

Economic searches

The health economic searches for this review question were broader to capture relevant health economic papers.

Databases: Ovid MEDLINE(R) ALL

Date of last search: 15/09/2022

#	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,kf.
8	or/4-7
9	3 or 8
10	exp Folic Acid/
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	10 or 11
13	9 and 12
14	Health Knowledge, Attitudes, Practice/ or preconception care/ or prenatal care/ or Health Behavior/
15	Information centers/ or information services/ or information dissemination/
16	Education/ or health education/ or exp consumer health information/ or Health Promotion/
17	(advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*).ti,ab,kf.
18	patient education as topic/ or Correspondence as Topic/ or Posters as Topic/
19	(letter* or correspond* or mail or poster*).ti,ab,kf.
20	exp Communication/
21	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write).ti,ab,kf.
22	exp Mass Media/
23	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*).ti,ab,kf.
24	Informed Consent/
25	(informed adj4 (consent or choice* or decision*)).ti,ab,kf.
26	Reminder Systems/
27	(recall or remind* or prompt* or nudge).ti,ab,kf.
28	(electronic* adj4 invit*).ti,ab,kf.
29	exp internet/ or exp computers, handheld/ or exp Cell Phone/ or mobile applications/ or electronic mail/ or hotlines/

#	Searches
30	((medical or health or electronic or virtual) adj4 (communicat* or educat* or informat* or learn* or coach*)).ti.
31	patient education handout/
32	exp teaching materials/
33	pamphlets/
34	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*).ti.
35	((online or web or internet or digital* or video*) adj3 (based or application* or intervention* or program* or therap*)).ab.
36	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) adj3 (based or application* or intervention* or device* or technolog* or program* or therap*)).ti,ab.
37	(computer* adj4 (handheld or palm top or palmtop or pda or tablet*)).ti.
38	(mobile health or mhealth or m health or ehealth or e health).ti.
39	((mobile health or mhealth or m health or ehealth or e health) adj3 (based or application* or intervention* or program* or therap*)).ab.
40	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?).ti,ab,kf.
41	exp Socioeconomic Factors/
42	health status/ or exp health inequities/
43	((government* or welfare or aid* or social security or relief) adj2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)).ti,ab,kf.
44	Health Services Accessibility/
45	((sexual or health) adj2 (clinic* or center* or centre*)).ti,ab,kf.
46	((preconcept* or pre concept* or prepregnan* or pre pregnan*) adj2 (clinic* or center* or centre* or service? or assessment*)).ti,ab,kf.
47	Community Networks/ or Community-Institutional Relations/
48	((communit* or social) adj4 (network* or relation* or support*)).ti,ab,kf.
49	social support/ or self-help groups/ or Peer Influence/
50	(group* adj2 (support* or self-help*)).ti,ab,kf.
51	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) adj4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)).ti,ab,kf.
52	Mentors/
53	(mentor* or role model*).ti,ab,kf.
54	House Calls/
55	((house or home) adj4 (call* or visit*)).ti,ab,kf.
56	Choice Behavior/ or Decision Making/ or Decision Support Techniques/
57	(decision* adj4 (making or support* or aid*)).ti,ab,kf.
58	risk reduction behavior/ or Motivation/ or "Patient Acceptance of Health Care"/
59	((behavio?r* or lifestyle* or life style*) adj2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)).ti,ab,kf.
60	motivat*.ti,ab,kf.
61	exp psychotherapy/ or exp counseling/ or self care/
62	self care.ti,ab,kf.
63	counsel*.ti,ab,kf.
64	((diet* or nutrient* or nutrition* or lifestyle*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.

#	Searches
65	((behavio?r* or cogniti* or psycho*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
66	or/14-65
67	13 and 66
68	letter/
69	editorial/
70	news/
71	exp historical article/
72	Anecdotes as Topic/
73	comment/
74	case reports/
75	(letter or comment*).ti.
76	or/68-75
77	randomized controlled trial/ or random*.ti,ab.
78	76 not 77
79	animals/ not humans/
80	exp Animals, Laboratory/
81	exp Animal Experimentation/
82	exp Models, Animal/
83	exp Rodentia/
84	(rat or rats or mouse or mice or rodent*).ti.
85	or/78-84
86	67 not 85
87	limit 86 to English language
88	Economics/
89	Value of life/
90	exp "Costs and Cost Analysis"/
91	exp Economics, Hospital/
92	exp Economics, Medical/
93	exp Resource Allocation/
94	Economics, Nursing/
95	Economics, Pharmaceutical/
96	exp "Fees and Charges"/
97	exp Budgets/
98	budget*.ti,ab.
99	cost*.ti,ab.
100	(economic* or pharmaco?economic*).ti,ab.
101	(price* or pricing*).ti,ab.
102	(financ* or fee or fees or expenditure* or saving*).ti,ab.
103	(value adj2 (money or monetary)).ti,ab.
104	resourc* allocat*.ti,ab.
105	(fund or funds or funding* or funded).ti,ab.
106	(ration or rations or rationing* or rationed).ti,ab.
107	ec.fs.
108	or/88-107
109	exp models, economic/
110	*Models, Theoretical/
111	*Models, Organizational/
112	markov chains/
113	monte carlo method/

#	Searches
114	exp Decision Theory/
115	(markov* or monte carlo).ti,ab.
116	econom* model*.ti,ab.
117	(decision* adj2 (tree* or analy* or model*)).ti,ab.
118	or/109-117
119	quality-adjusted life years/
120	sickness impact profile/
121	(quality adj2 (wellbeing or well being)).ti,ab.
122	sickness impact profile.ti,ab.
123	disability adjusted life.ti,ab.
124	(qal* or qtime* or qwb* or daly*).ti,ab.
125	(euroqol* or eq5d* or eq 5*).ti,ab.
126	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
127	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
128	(hui or hui1 or hui2 or hui3).ti,ab.
129	(health* year* equivalent* or hye or hyes).ti,ab.
130	discrete choice*.ti,ab.
131	rosser.ti,ab.
132	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
133	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
134	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
135	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
136	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
137	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
138	or/119-137
139	87 and (108 or 118 or 138)

Databases: Embase

Date of last search: 15/09/2022

#	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,kf.
8	or/4-7
9	3 or 8
10	folic acid/
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	10 or 11
13	9 and 12
14	attitude to health/ or prepregnancy care/ or prenatal care/ or health behavior/
15	information center/ or information service/ or information dissemination/
16	(advi?e* or promot* or educat* or knowledge or intervention* or coach* or mentor* or inform* or aware* or disseminat*).ti,ab,kf.
17	patient education/ or writing/ or publication/

#	Searches
18	(letter* or correspond* or mail or poster*).ti,ab,kf.
19	exp interpersonal communication/
20	(communic* or messag* or listen* or negotiat* or persua* or dialogu* or conversation* or question* or discuss* or written or write).ti,ab,kf.
21	mass medium/
22	(media or radio* or television* or tv* or broadcast* or podcast* or newspaper* or magazine* or display* or presentation*).ti,ab,kf.
23	informed consent/
24	(informed adj4 (consent or choice* or decision*)).ti,ab,kf.
25	reminder system/
26	(recall or remind* or prompt* or nudge).ti,ab,kf.
27	(electronic* adj4 invit*).ti,ab,kf.
28	exp internet/ or personal digital assistant/ or exp mobile phone/ or exp mobile application/ or e-mail/ or hotline/
29	((medical or health or electronic or virtual) adj4 (communicat* or educat* or informat* or learn* or coach*)).ti.
30	exp teaching/
31	(app or apps or blog* or banner or booklet* or brochure* or bulletin* or cellphone* or diary or diaries or digital* or dvd* or elearn* or e learn* or email* or e mail* or electronic mail* or facebook or face book or facetime or face time or factsheet* or forum* or flyer or guidebook* or handout* or hand out* or helpline* or hotline* or internet* or ipad* or iphone* or leaflet* or myspace or online or magazine* or mobile phone* or multimedia messag* or newsletter* or pamphlet* or palm pilot* or personal digital assistant* or phone* or pocket pc* or podcast* or postcard* or poster? or skype* or smartphone* or smart phone* or smartwatch* or smart watch* or social media or social network* or sms or telephone* or text messag* or twitter or tweet* or video* or web* or wiki* or youtube*).ti.
32	((online or web or internet or digital* or video*) adj3 (based or application* or intervention* or program* or therap*)).ab.
33	((phone* or telephone* or smartphone* or cellphone* or smartwatch* or mobile* or portable*) adj3 (based or application* or intervention* or device* or technolog* or program* or therap*)).ti,ab.
34	(computer* adj4 (handheld or palm top or palmtop or pda or tablet*)).ti.
35	(mobile health or mhealth or m health or ehealth or e health).ti.
36	((mobile health or mhealth or m health or ehealth or e health) adj3 (based or application* or intervention* or program* or therap*)).ab.
37	(cap* or pearl* or softgel* or gel* or pill* or tab* or lozenge* or pastille* or pellet* or liquid* or drink* or solution* or juice* or fluid* or drop* or powder* or sherbet* or biscuit* or bar?).ti,ab,kf.
38	exp socioeconomics/
39	health status/ or health disparity/
40	((government* or welfare or aid* or social security or relief) adj2 (support* or sponsor* or grant* or scheme* or program* or provide* or provision* or assist* or gift* or handout* or donat* or voucher* or subsid* or intervent*)).ti,ab,kf.
41	health care access/
42	((sexual or health) adj2 (clinic* or center* or centre*)).ti,ab,kf.
43	((preconcept* or pre concept* or prepregnan* or pre pregnan*) adj2 (clinic* or center* or centre* or service? or assessment*)).ti,ab,kf.
44	community care/ or public relations/
45	((communit* or social) adj4 (network* or relation* or support*)).ti,ab,kf.
46	social support/ or self help/ or peer pressure/
47	(group* adj2 (support* or self-help*)).ti,ab,kf.
48	((peer* or family or families or friend* or professional* or physician* or nurse*1 or health visitor* or midwife or midwives or social worker* or leader* or community or communities or teacher* or faith or pharmacy* or pharmacist* or chemist or pharmacies* or GP*1 or practition* or doctor* or health professional* or clinician* or consultant* or primary-care* or dietician* or nutritionist* or HCP*1) adj4 (influence* or pressure* or recommend* or advice or advise* or led or support* or educ* or advocat* or knowledge or inform*)).ti,ab,kf.
49	mentor/
50	(mentor* or role model*).ti,ab,kf.
51	home visit/
52	((house or home) adj4 (call* or visit*)).ti,ab,kf.
53	decision making/ or decision support system/

#	Searches
54	(decision* adj4 (making or support* or aid*)).ti,ab,kf.
55	risk reduction/ or motivation/ or patient attitude/
56	((behavio?r* or lifestyle* or life style*) adj2 (change* or changing or modification* or modify or modifying or therapy or therapies or program* or intervention* or technique* or establish* or individual* or improv* or enhanc* or encourag* or promot* or optimiz* or optimis* or incentiv*)).ti,ab,kf.
57	motivat*.ti,ab,kf.
58	exp psychotherapy/ or exp counseling/ or self care/
59	self care.ti,ab,kf.
60	counsel*.ti,ab,kf.
61	((diet* or nutrient* or nutrition* or lifestyle*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
62	((behavio?r* or cogniti* or psycho*) adj2 (therap* or treat* or intervention* or strateg* or session* or modif* or training or support* or aid* or help* or program*)).ti,ab,kf.
63	or/14-62
64	13 and 63
65	letter.pt. or letter/
66	note.pt.
67	editorial.pt.
68	case report/ or case study/
69	(letter or comment*).ti.
70	or/65-69
71	randomized controlled trial/ or random*.ti,ab.
72	70 not 71
73	animal/ not human/
74	nonhuman/
75	exp Animal Experiment/
76	exp Experimental Animal/
77	animal model/
78	exp Rodent/
79	(rat or rats or mouse or mice or rodent*).ti.
80	or/72-79
81	64 not 80
82	limit 81 to English language
83	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
84	82 not 83
85	health economics/
86	exp economic evaluation/
87	exp health care cost/
88	exp fee/
89	budget/
90	funding/
91	resource allocation/
92	budget*.ti,ab.
93	cost*.ti,ab.
94	(economic* or pharmaco?economic*).ti,ab.
95	(price* or pricing*).ti,ab.
96	(financ* or fee or fees or expenditure* or saving*).ti,ab.
97	(value adj2 (money or monetary)).ti,ab.
98	resourc* allocat*.ti,ab.
99	(fund or funds or funding* or funded).ti,ab.
100	(ration or rations or rationing* or rationed).ti,ab.

#	Searches
101	or/85-100
102	statistical model/
103	exp economic aspect/
104	102 and 103
105	*theoretical model/
106	*nonbiological model/
107	stochastic model/
108	decision theory/
109	decision tree/
110	monte carlo method/
111	(markov* or monte carlo).ti,ab.
112	econom* model*.ti,ab.
113	(decision* adj2 (tree* or analy* or model*)).ti,ab.
114	or/104-113
115	quality adjusted life year/
116	"quality of life index"/
117	short form 12/ or short form 20/ or short form 36/ or short form 8/
118	sickness impact profile/
119	(quality adj2 (wellbeing or well being)).ti,ab.
120	sickness impact profile.ti,ab.
121	disability adjusted life.ti,ab.
122	(qal* or qtime* or qwb* or daly*).ti,ab.
123	(qal* or qtime* or qwb* or daly*).ti,ab.
124	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
125	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
126	(hui or hui1 or hui2 or hui3).ti,ab.
127	(health* year* equivalent* or hye or hyes).ti,ab.
128	discrete choice*.ti,ab.
129	rosser.ti,ab.
130	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
131	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
132	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
133	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
134	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
135	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
136	or/115-135
137	84 and (101 or 114 or 136)

Database: CRD HTA (last updated 31st March 2018)

Date of last search: 12/09/2022

#	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

#	Searches
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 EXPLODE ALL TREES IN HTA
13	(((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
14	#12 OR #13
15	#11 AND #14

Database: INAHTA

Date of last search: 12/09/2022

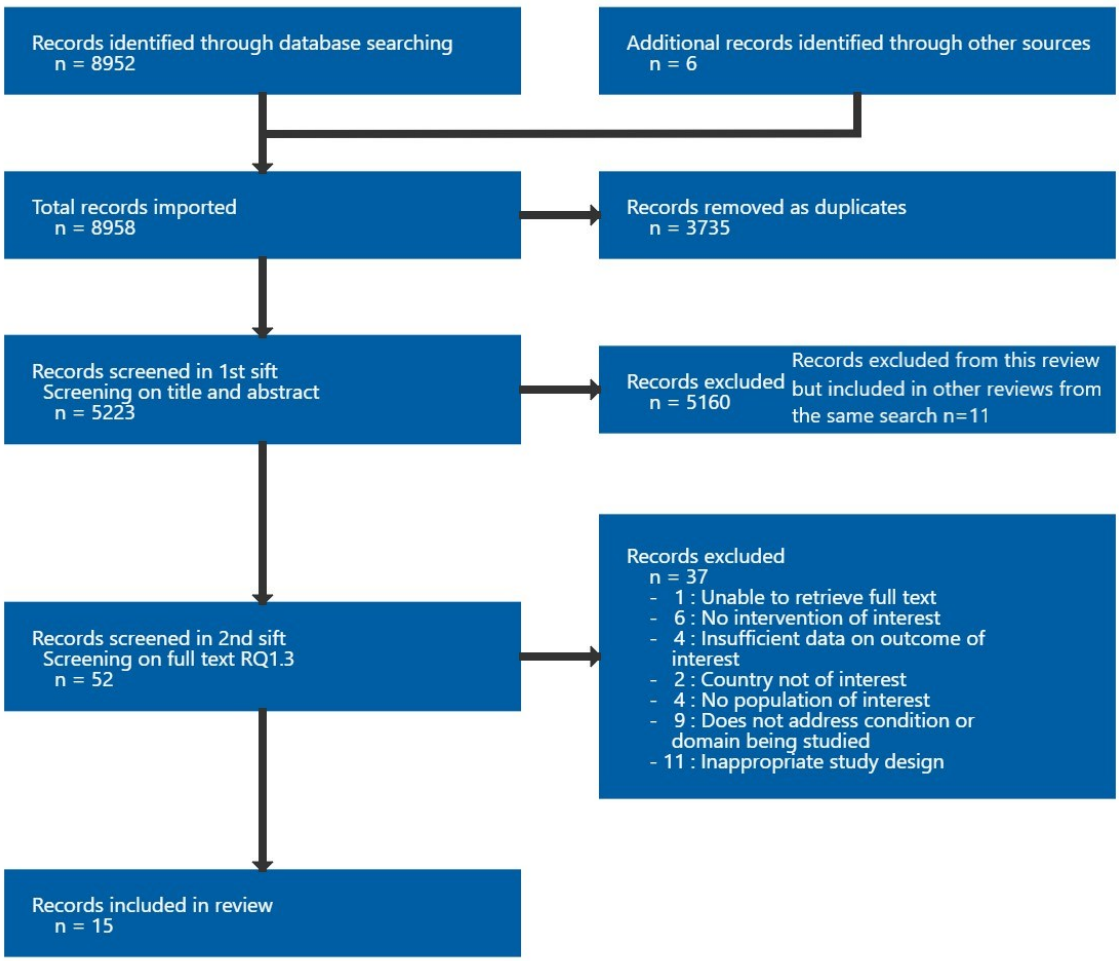
#	Searches
1	"Pregnancy"[mhe]
2	"Pregnant Women"[mh]
3	"Prenatal Care"[mh]
4	((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[Title] OR ((antenatal* or ante natal* or gestation* or maternal* or mother* or pregnan* or prenatal* or pre natal*))[abs]
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"[mhe]
13	((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]
14	#12 OR #13
15	#11 AND #14

Appendix C Effectiveness evidence study selection

Study selection for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

One literature search was performed for the review questions [C] and [E]. The flow chart below includes full texts considered for inclusion in this review only.

Figure 1: Effectiveness evidence study selection flow chart



Appendix D Evidence tables

Evidence tables for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Table 5: Evidence tables

Anwar, 2011

Bibliographic Reference	Anwar, Ayesha; Salih, Amira; Masson, Ewan; Allen, Belinda; Wilkinson, Linda; Lindow, Stephen W; The effect of pre-pregnancy counselling for women with pre-gestational diabetes on maternal health status.; European journal of obstetrics, gynecology, and reproductive biology; 2011; vol. 155 (no. 2); 137-9

Study details

Country/ies where study was carried out	United Kingdom
Study type	Uncontrolled before-and-after study
Study dates	1997 - 2007
Inclusion criteria	• diabetic women • attended a pre-pregnancy care clinic • subsequently achieved pregnancy in the decade 1997–2007

Exclusion criteria	Not reported
Patient characteristics	**Age, mean (range), years** 28.5 (19-40) **Gravidity, mean (range)** 1.9 (1 - 8) **Parity, mean (range)** 0.7 (0 - 4) **Time between PPC and booking, mean (range), months** 7.0 (0.2 - 47) **Duration of diabetes, mean (range), years** 10.9 (0.1 - 37)
Intervention(s)/control	**Intervention: Pre-pregnancy counselling (PPC)** PPC occurred in a multidisciplinary medical and obstetric clinic held in Hull and East Yorkshire Women and Children's Hospital. The team consisted of a consultant obstetrician, consultant physician, diabetes specialist nurse and a dietician. The clinic held weekly and follow-up appointments were made when necessary.

	Essential components included: 1. Review and consideration of medical conditions, drug treatment, smoking and alcohol use. 2. Review of the obstetric and gynaecological history. 3. Advice on glycaemic control to optimise HbA1c levels and organised screening for diabetic complications. No further information on folic acid advice reported in the paper. **Comparator:** Data recorded at the booking visit when pregnancy was achieved.
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Sample size	N = 57
Other information	All the case notes of women who attended PPC and subsequently become pregnant during study period were reviewed (total = 57). The data was recorded on a proforma which had two separate sections: one for the PPC visit and one for the booking visit when a pregnancy was achieved. The study did not adjust for confounders.

HbA1c: haemoglobin A1C; PPC: pre-pregnancy care counselling.

Study arms

Intervention arm: pre-pregnancy care (n = 57)

Outcomes

Study timepoints

Baseline

- 8 weeks (Study reported timepoint as "at booking")

Folic acid use

Outcome	Intervention arm: pre-pregnancy care, Baseline, n = 57	Intervention arm: pre-pregnancy care, 8 weeks , n = 57
Folic acid use (n (%)) No of events	n = 18; % = 32	n = 48; % = 89

n: number of participants.

Folic acid use - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding variables)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Self-reported outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

Chilukuri, 2018

Bibliographic Reference	Chilukuri, Nymisha; Cheng, Tina L; Psoter, Kevin J; Mistry, Kamila B; Connor, Katherine A; Levy, Daniel J; Upadhya, Krishna K; Effectiveness of a Pediatric Primary Care Intervention to Increase Maternal Folate Use: Results from a Cluster Randomized Controlled Trial.; The Journal of pediatrics; 2018; vol. 192; 247-252e1

Study details

Country/ies where study was carried out	USA
Study type	Cluster randomised controlled trial
Study dates	October 2013 to March 2015
Inclusion criteria	• biologic mothers presenting with their child less than 12 months of age for pediatric well-care • capable of completing assessments in English or Spanish • recruited from October 2013 to March 2015.
Exclusion criteria	• women known to be pregnant at the time of the visit
Patient characteristics	**Age of mother (mean, SD), years** Intervention group = 26.5 (6.2) Control group = 26.4 (6.0) **Previous live birth, (mean, SD)** Intervention group = 2.08 (1.25) Control group = 1.95 (1.21) **Pregnancy intention in the next 6 months, n (%)**

	Intervention group = 3 (1.5) Control group = 9 (4.1) **Race, n (%)** Hispanic Intervention group = 11 (5.0) Control group = 8 (4.1) African American, non-Hispanic Intervention group = 177 (81.2) Control group = 170 (86.3) White, non-Hispanic Intervention group = 17 (7.8) Control group = 9 (4.6) Other, non-Hispanic Intervention group = 13 (6.0)

	Control group = 10 (5.1)
Intervention(s)/control	Intervention: Focused counselling which included 1. Receipt of Centers for Disease Control and Prevention (CDC) preconception women's health handout entitled “Show Your Love, Steps to a Healthier Me,” a community resource listing. 2. A 90- day supply of multivitamins with 400 µg of folate. 3. Completion of a 15-item preconception health screener that assessed exposure to primary health and behavioural preconception risk factors (including folate intake) as identified by the CDC. 4. Tailored counselling. Control: No focused counselling which included 1. Receipt of CDC preconception women's health handout entitled “Show Your Love, Steps to a Healthier Me,” a community resource listing. 2. A 90- day supply of multivitamins with 400 µg of folate.
Duration of follow-up	6 months
Sources of funding	Not industry funded
Sample size	N = 415 Design effect = 1 + (4-1) x 0.027 =1.081 Adjusted sample size = 415/1.081 = 384

Other information	Outcomes self-reported via approximately 30-minute telephone interview. Follow-up data collected at 6 months but if participant was unreachable, attempts continued for up to 2 months after the due date. Not stated if mothers had become pregnant at follow up.

µg: micrograms; n: number of participants; SD: Standard deviation; USA: United States of America.

Study arms

Intervention arm: Focused counselling (n = 197)

Control arm: No focused counselling (n = 218)

Outcomes

Study timepoints

- 6 month

Comparison of daily folate use between study groups at 6 months follow-up with baseline (n = 352)

Outcome	Intervention arm: Focused counselling, 6 month, n = 163	Control arm: No focused counselling, 6 month, n = 189
Daily folate use (odds ratio) Adjusted Odds Ratio (95% CI)	2.04 (1.04 to 3.98)	Referent

CI: confidence interval; n: number of participants.

Daily folate use - Polarity - Higher values are better

Adjusted for age of the mother, age of the child, race/ethnicity, education, income, parity, and intention to have a pregnancy in the next 6 months. Models also accounted for clustering of individuals by provider and within sites.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cluster randomised trials NGA

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
1b. Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation	Risk of bias judgement for the timing of identification and recruitment of individual participants in relation to timing of randomisation	Low
2a. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Some concerns (Some concerns *about whether participants were analysed in a different group from their original cluster, for example, if patient changed clinician during the study)*
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(No information whether data was available for all clusters and 15% loss to follow-up without adequate analysis to account for it)*
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(Some concerns around self-reported outcomes as assessment of outcome was likely to be influenced*

		by knowledge of intervention received)
5. Bias in selection of the reported result	Risk of bias 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 in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable

de Weerd, 2002

Bibliographic Reference	de Weerd, S; Thomas, CMG; Cikot, RJL; Steegers-Theunissen, RPM; de Boo, TM; Steegers, EAP; de Weerd, Sabina; Thomas, Chris M G; Cikot, Rolf J L M; Steegers-Theunissen, Régine P M; de Boo, Theo M; Steegers, Eric A P; Preconception counseling improves folate status of women planning pregnancy.; Obstetrics & Gynecology; 2002; vol. 99 (no. 1); 45-50

Study details

Country/ies where study was carried out	The Netherlands
Study type	Uncontrolled before-and-after study
Study dates	September 1997 to April 1999

Inclusion criteria	• couples with a scheduled appointment at the fertility clinic (because of the inability to become pregnant within 1 year) or at the clinic for preconception care (because of previous obstetric complications or other maternal risk factors) of the University Medical Center Nijmegen
Exclusion criteria	• Pregnant women
Patient characteristics	**Age, n (%), years** 25-29 = 23 (20.7) 30–34 = 55 (49.5) 35–39 = 31 (27.9) ≥40 = 2 (1.8) **Obstetric history, n (%)** Never pregnant = 66 (59.5) Prior birth = 36 (32.4) Patient characteristics were not reported by group
Intervention(s)/control	Intervention: counselling involving: • Discussion on relevant aspects of health promotion which included smoking cessation, nutritional habits, antenatal care, and folic acid supplement intake.

	• Advised to take a multivitamin supplement containing 400µg of folic acid until 8 weeks after conception • Provision of the multivitamin supplement.
Duration of follow-up	16 months
Sources of funding	Not industry funded
Sample size	N=111
Other information	Study reports red cell folate and serum folate at baseline, 4 and 12 months in users and non-users of folate pre-intervention, as well as red cell folate and serum folate at certain thresholds. Serum folate levels at 4 months was used in analysis as this is the closest timepoint to when folic acid consumption is expected. Additionally, only data non-folate users pre-conception has been reported to get a more accurate association between the intervention and outcome. Study did not adjust for confounders.

µg: micrograms; n: number of participants.

Study arms

Folate non-users pre-counselling (n = 52)

Outcomes

Study timepoints

- baseline
- 4 month

Folate status before and 4 months after counselling

Outcome	Folate non-users pre-counselling, Baseline, n = 52	Folate non-users pre-counselling, 4 month, n = 52
Serum Folate (nmol/L) (mean (SE)) Mean (SE)	18.7 (1.3)	20.8 (1.9)

n: number of participants; nmol/L: nanomoles Per Liter; SE: standard error.

Red cell folate (nmol/L) - Polarity - Higher values are better
Serum Folate (nmol/L) - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate (No adjustment for confounding factors)
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate (Some participants lost to follow up and results were not robust to the presence of missing data)
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate (The study is judged to raise moderate risk of bias due ot moderate concerns in 2 domains)

Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

deRosset, 2014

Bibliographic Reference	deRosset, Leslie; Mullenix, Amy; Flores, Alina; Mattia-Dewey, Daniel; Mai, Cara T.; Promotora de Salud: Promoting Folic Acid Use Among Hispanic Women.; Journal of'Women's Health (15409996); 2014; vol. 23 (no. 6); 525-531

Study details

Country/ies where study was carried out	USA
Study type	Uncontrolled before-and-after study
Study dates	November 2009 to July 2010
Inclusion criteria	• non-pregnant female • reported being capable of pregnancy • Spanish-speaking

	• between the ages of 18–45 years • living in either Wake or Johnston counties • reported not having received education from the Campaign within the year prior to the implementation of this intervention (2008–2009)
Exclusion criteria	Not reported
Patient characteristics	**Age, (mean, SD), years** Participants who completed study = 30 (7.6) Participants lost to follow-up = 31 (6.6) **Ever had children, %** Participants who completed study: Yes = 87 No = 13 Participants lost to follow-up: Yes = 84 No = 16
Intervention(s)/control	**Intervention:** an educational intervention workshop consisting of:

	• Educational information about folic acid, vitamins, and the prevention of neural tube defects (NTD)s. • Spanish-language educational brochures. • A 90-day supply of multivitamins containing 400 µg folic acid. • A small promotional item (pen, mirror and brush, and so on)
Duration of follow-up	4 months
Sources of funding	Not industry funded
Sample size	N = 303
Other information	Post-intervention surveys were conducted verbally over the telephone, except when participant could not be reached via telephone, then, the survey was completed at the participant's home in person. Study reports other measures of knowledge but only the most relevant that can be standardised across studies have been extracted and reported. Study did not adjust for confounders.

µg: micrograms; SD: standard deviation; USA: United States of America.

Study arms

Intervention arm: educational workshop (n = 386)

Outcomes

Study timepoints

- baseline
- 4 month

Knowledge of folic acid

Outcome	Intervention arm: educational workshop, Baseline, n = 303	Intervention arm: educational workshop, 4 month, n = 303
Knowledge that folate prevents birth defects (%) No of events	% = 82	% = 92
Knowledge that folic acid is important to women of childbearing age (%) Which vitamins or mineral supplements do you think are very important to women of childbearing age? No of events	% = 85	% = 94

n: number of participants.

Knowledge that folate prevents birth defects - Polarity - Higher values are better
Knowledge that folic acid is important to women of childbearing age - Polarity - Higher values are better
Study only reported on participants that completed the follow-up.

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Some missing data for participants and results were not robust to the presence of missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Self-reported outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(The study is judged to raise moderate risk of bias due to moderate concerns in 3 domains)*
Overall bias	Risk of bias variation across outcomes	N/A

Section	Question	Answer
Overall bias	Directness	Directly applicable

N/A: not applicable; p: probability.

Flores, 2017

Bibliographic Reference	Flores, Alina L.; Isenburg, Jennifer; Hillard, Christina L.; deRosset, Leslie; Colen, Lisa; Bush, Troy; Mai, Cara T.; Folic Acid Education for Hispanic Women: The Promotora de Salud Model.; Journal of Women's Health (15409996); 2017; vol. 26 (no. 2); 186-194

Study details

Country/ies where study was carried out	USA
Study type	Uncontrolled before-and-after study
Study dates	Not reported
Inclusion criteria	1. Hispanic women 2. predominantly spoke Spanish

	3. lived in one of the selected counties - Harris county, Texas, Hillsborough county, Florida, Cook county, Illinois and Mecklenburg county, North Carolina 4. were between the ages of 18 and 45 years at the start of the study.
Exclusion criteria	Not reported
Patient characteristics	**Age, n (%), years** <35 = 816 (57) ≥35 = 610 (43) Mean age = 33 **Previous child, n (%)** Yes = 1242 (87) No = 172 (12)
Intervention(s)/control	Intervention: 1 to 2 hours educational session about folic acid and neural tube defects and a 90-day supply of multivitamins containing folic acid.
Duration of follow-up	4 months after education session (1 month completion of multivitamin supply)
Sources of funding	Not industry funded
Sample size	N = 1756
Other information	Study reports other measures of knowledge but only the most relevant that can be standardised across studies have been extracted and reported.

	Study did not adjust for confounders.

n: number of participants; USA: United States of America.

Outcomes

Study timepoints

- baseline
- 4 month

Folic acid intake and knowledge before and after intervention

Outcome	**Study, Baseline, n = 1426**	**Study, 4 month, n = 1426**
Folic acid intake (n (%)) No of events	n = 69; % = 5	n = 784; % = 55
Folic acid knowledge (n (%)) Question: Which vitamins or mineral supplements do you think are important to women of childbearing age? Only reports those that answered folic acid No of events	n = 1065; % = 75	n = 1314; % = 92
Folic acid prevents birth defects What have you read, seen or heard about folic acid? Only reporting for those that answered 'it prevents birth defects' No of events	n = 583; % = 41	n = 1178; % = 83

Outcome	Study, Baseline, n = 1426	Study, 4 month, n = 1426
Timing of taking folic acid When should a woman take folic acid? Only reporting for those that answered 'before she gets pregnant' No of events	n = 458; % = 32	n = 401; % = 28

n: number of participants.

Folic acid intake - Polarity - Higher values are better

Folic acid knowledge - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Unclear information on missing data. No information provided on number of participants recruited into the study. Study reports on participants eligible and participants who completed intervention and post-intervention survey.)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Self-reported outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(The study is judged to raise high risk of bias due to some concerns in 3 domains)*
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

Geyer, 2022

Bibliographic Reference	Geyer, K.; Gunther, J.; Hoffmann, J.; Spies, M.; Raab, R.; Zhelyazkova, A.; Rose, I.; Hauner, H.; Dietary Supplementation Before, during and after Pregnancy: Results of the Cluster-Randomized GeliS Study; Geburtshilfe und Frauenheilkunde; 2022; vol. 82 (no. 7); 736-746

Study details

Country/ies where study was carried out	Germany
Study type	Cluster randomised controlled trial
Study dates	2013 to 2015
Inclusion criteria	• pregnant women before 12 weeks of gestation • aged between 18 and 43 • had a body mass index between 18.5 and 40.0 kg/m^2 • sufficient German language skills • had given their written informed consent.
Exclusion criteria	• multiple pregnancies • high-risk pregnancies • severe illnesses that interfered with the adherence to the study protocol.

	• further causes for exclusion of study participants in the course of the intervention phase were miscarriage, severe pregnancy complications, abortion, or maternal death.
Patient characteristics	**Pre-pregnancy age (mean, SD), years** Intervention group = 30.1 (4.3) Control group = 30.3 (4.6) **Primiparous, n (%)** Intervention group = 661 (62.4) Control group = 556 (53.6) **Pre pregnancy BMI, n (%)** BMI 18.5–24.9 kg/m^2: Intervention group = 685 (64.6) Control group = 687 (66.1) BMI 25.0–29.9 kg/m^2: Intervention group = 251 (23.7)

	Control group = 225 (21.7) BMI 30.0–40.0 kg/m^2: Intervention group = 124 (11.7) Control group = 127 (12.2)
Intervention(s)/control	**Intervention:** Lifestyle counselling encompassing • The topics of a healthy diet and dietary supplementation during pregnancy and the breastfeeding period. • Physical activity as well as appropriate weight gain during pregnancy. • All contents of the lifestyle counselling were based on the recommendations of the network “Healthy Start – Young Family Network” presented with the help of standardized presentation boards, teaching kits, and brochures. **Control:** Routine medical examinations during pregnancy, along with a flyer and brochures with brief and general information on a healthy lifestyle during pregnancy. Specially trained staff in the medical practices, including medical assistants, midwives, and gynecologists, held lifestyle counselling sessions at gestational weeks 12–16, 16–20, and 30– 34. An additional counselling session took place after birth (6– 8 weeks postpartum).
Duration of follow-up	Until end of first trimester. Counselling sessions were repeated at intervals until 6 to 8 weeks postpartum
Sources of funding	Not industry funded
Sample size	N = 10 clusters, 2099 participants Design effect not calculated because study reports adjusted estimates

Other information	Primary aim was to decrease the proportion of women who gained excessive weight during pregnancy but also investigated whether lifestyle counselling based on the recommendations of healthy start - Young family network would improve supplementation behaviour of women during and after pregnancy. Data was reported at various timepoints from before pregnancy to postpartum but only the timepoint most relevant to this review has been extracted and reported. Study was part of the “Gesund leben in der Schwangerschaft” (GeliS; “Healthy living in pregnancy”) trial. Study adjusted for pre-pregnancy BMI category, age, educational level and parity.

BMI: Body mass index; kg: kilograms; m: metres; n: number of participants; SD: Standard deviation.

Study arms

Intervention arm: Lifestyle counselling (n = 1060)

n=5 clusters n=1060 participants

Control arm: Routine medical examinations (n = 1039)

n=5 clusters n=1039 participants

Outcomes

Study timepoints

- 12 week (First trimester)

Supplementation of folic acid before and during pregnancy

Outcome	12 week, Intervention arm: Lifestyle counselling, n = 1052, 5 clusters	12 week, Control arm: Routine medical examinations, n = 1039, 5 clusters
Folic acid supplementation (odds ratio) Adjusted odds ratio (95% CI)*	1.10 (0.93 to 1.31)	Referent

CI: confidence interval; n: number of participants.

Folic acid supplementation - Polarity - Higher values are better

*adjusted for pre-pregnancy BMI category, age, educational level and parity

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cluster randomised trials NGA

Section	Question	Answer
1a. Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(No information on the randomisation process*)
1b. Bias arising from the timing of identification and recruitment of individual participants in relation to timing of randomisation	Risk of bias judgement for the timing of identification and recruitment of individual participants in relation to timing of randomisation	Some concerns *(No information on identification and recruitment of participants in relation to timing of randomisation but baseline characteristics do not suggest that there is a problem)*
2a. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Some concerns *(Insufficient information to assess the effect of assignment to intervention and deviations from assigned intervention)*

Section	Question	Answer
3. Bias due to missing outcome data	Risk of bias judgement for missing outcome data	Some concerns *(No evidence that analysis of results accounted for missing outcome data)*
4. Bias in measurement of the outcome	Risk of bias judgement for measurement of the outcome	Some concerns *(Self-reported outcomes and it is unclear if participants were aware of the intervention)*
5. Bias in selection of the reported result	Risk of bias for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(The study is judged to raise high risk of bias due to some concerns in most domains.)*
Overall bias and Directness	Overall Directness	Partially applicable *(Intervention is indirect due to the primary aim being to decrease the proportion of women who gained excessive weight during pregnancy.)*

Holmes, 2017

Bibliographic Reference	Holmes, V.A.; Hamill, L.L.; Alderdice, F.A.; Spence, M.; Harper, R.; Patterson, C.C.; Loughridge, S.; McKenna, S.; Gough, A.; McCance, D.R.; Effect of implementation of a preconception counselling resource for women with diabetes: A population based study; Primary Care Diabetes; 2017; vol. 11 (no. 1); 37-45

Study details

Country/ies where study was carried out	Northern Ireland
Study type	Uncontrolled before-and-after study
Study dates	October 2010 to December–2010 for distribution of DVDs June 2011 to May–2012 for recruitment of participants to intervention group 1 September 2009 to 31 August–2010 for recruitment of participants to control group (pre-DVD cohort)
Inclusion criteria	Women with pre-gestational diabetes who: • delivered/were expected to deliver between February 2012 and January 2013 (became pregnant 5 months after DVD distribution - first day of last menstrual period on or after 1st June 2011) • attended one of the five joint diabetes-antenatal clinics in Northern Ireland.
Exclusion criteria	Not reported
Patient characteristics	**Age (mean, SD), years** Pre DVD = 30.9 (6.5) Viewed DVD = 32.0 (4.7) **Type of diabetes, n (%)** Type 1:

	Pre DVD = 88 (77.2) Viewed DVD = 50 (86.2) Type 2: Pre DVD = 26 (22.8) Viewed DVD = 8 (13.8) **Nulliparous, n (%)** Pre DVD = 52 (45.6) Viewed DVD = 23 (39.7) **Diabetes duration (mean, SD), year** Pre DVD = 12.0 (8.5) Viewed DVD = 15.6 (8.8)
Intervention(s)/control	**Intervention:** Preconception counselling DVD comprising: 1. Forty-five minutes information on the importance of planning for pregnancy and on essential pregnancy planning advice in the form of a pre-pregnancy checklist **Control:** No preconception counselling DVD (usual care pre implementation of preconception counselling DVD)

Duration of follow-up	5 months
Sources of funding	Not industry funded
Sample size	N = 249
Other information	Comparison group was selected from data available from a regional audit of the same five regional joint diabetes-antenatal clinics across Northern Ireland, involving all deliveries or expected deliveries in women with pre-gestational diabetes between 1st September 2009 and 31st August 2010. Additional group (those that received DVD) was reported in the study but did not contribute anything to this review and so was not extracted. Intervention group (viewed DVD) is a subset of those that received the DVD (that is, those that received it and watched it) Study adjusted for diabetes type, diabetes duration, parity, social deprivation, age and booking hospital

DVD: digital versatile disc; n: number of participants; SD: standard deviation.

Study arms

Control arm: Pre DVD implementation (n = 114)

Intervention arm: received and viewed preconception counselling DVD (n = 58)

Outcomes

Preconception folic acid supplementation

Outcome	Control arm: Pre DVD implementation, n = 114	Intervention arm: received and viewed preconception counselling DVD, n = 58
Folic acid intake preconception Mean Adjusted odds ratio (95% CI)	Referent	4.85 (1.94 to 12.11)
Taking 5mg folic acid preconception (where dose was recorded) Adjusted odds ratio (95% CI)	Referent	6.39 (0.93 to 44.07)

CI: confidence interval; DVD: digital versatile disc; n: number of participants;
Folic acid intake preconception - Polarity - Higher values are better
Taking 5mg folic acid preconception - Polarity - Higher values are better
Adjusted for diabetes type, diabetes duration, parity, deprivation, age, and booking hospital

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low

Section	Question	Answer
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	No information *(No information on missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	No information *(No information on who outcome assessors were so unable to establish level of bias.)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

Morgan 2009

Bibliographic Reference	Morgan. LM; Major J; Meyer R; Mullenix A; Multivitamin use among non-pregnant females of childbearing age in the Western North Carolina multivitamin distribution program; N C Med J; 2009; vol. 5 (no. 70); 386-90

Study details

Country/ies where study was carried out	USA
Study type	Uncontrolled before-and-after study
Study dates	October 2004 to December 2004
Inclusion criteria	Non pregnant females of childbearing age
Exclusion criteria	Not reported
Patient characteristics	**Age, n (%), years** <25 = 163 (51.6) 25-34 = 110 (34.8) >34 = 43 (13.6) No response = 6 (1.9) **Race, n (%)** White = 193 (60.3) Latino/Hispanic = 85 (26.6)

	African American = 24 (7.5) American Indian = 9 (2.8) Other/Unknown = 11 (3.4) Characteristics not reported by group
Intervention(s)/control	**Intervention:** a free 100-count bottle of multivitamins containing 400 mcg of folic acid from a health care provider (usually a nurse). Additional elements included: • Verbal counselling. • The provision of written materials, such as a brochure, explaining the importance of folic acid. • Free refill of folic acid vitamin when finished.
Duration of follow–up	8 - 10 months
Sources of funding	Not industry funded
Sample size	N = 500
Other information	Study did not adjust for confounders

mcg: microgram; n: number of participants; USA: United States of America.

Study arms

Intervention arm: verbal counselling and free folic acid supply (n = 500)

Outcomes

Study timepoints

- baseline
- 8 month (8 - 10 month follow up)

Changes in vitamin consumption behaviour

Outcome	Intervention arm: verbal counselling and free folic acid supply, Baseline, n = 500	Intervention arm: verbal counselling and free folic acid supply, 8 month, n = 322
Folic acid supplement intake everyday (%) All participants No of events	n = 82; % = 25.5	n = 172; % = 53.4

n: number of participants.

Folic acid supplement intake everyday - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding)*

Section	Question	Answer
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(35% loss to follow up. Results were not robust to be presence of missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Self-reported outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(The study is judged to raise high risk of bias due to moderate concerns in 3 domains)*
Overall bias	Risk of bias variation across outcomes	N/A

Section	Question	Answer
Overall bias	Directness	Directly applicable

mcg: microgram; N/A: not applicable.

Murphy, 2010

Bibliographic Reference	Murphy, H.R.; Roland, J.M.; Skinner, T.C.; Simmons, D.; Gurnell, E.; Morrish, N.J.; Soo, S.-C.; Kelly, S.; Lim, B.; Randall, J.; Thompsett, S.; Temple, R.C.; Effectiveness of a regional prepregnancy care program in women with type 1 and type 2 diabetes: Benefits beyond glycemic control; Diabetes Care; 2010; vol. 33 (no. 12); 2514-2520

Study details

Country/ies where study was carried out	UK
Study type	Prospective cohort study
Study dates	10th January 2006 to 31 September 2009
Inclusion criteria	• women between 16 and 45 years with type 1 and type 2 diabetes • attending specialist and primary care diabetes centres.
Exclusion criteria	Not reported
Patient characteristics	**Age (median years, 10-90th centile)**

	Intervention group (women who attended pre-pregnancy counselling (PPC)): 32 (26-39) Intervention group (women who did not attend PPC): 31 (22-39) **BMI at booking (median kg/m^2, 10-90th centile)** Intervention group (women who attended PPC): 26.1 (21.3-36.2) Intervention group (women who did not attend PPC): 27.9 (22.2-38.1) Patient characteristics of women in the control group (historical cohort from same centres who did not receive pre-pregnancy care) were not reported
Intervention(s)/control	Intervention group: pre-pregnancy care. Leaflets were sent to women with diabetes and relevant health centres disseminated relevant information regarding pre-pregnancy care Control group: historical cohort from same centres who did not receive pre-pregnancy care Intervention delivered by diabetes physician, specialist nurse, midwife, or obstetrician
Duration of follow-up	3 months
Sources of funding	Not reported
Sample size	N = 680 Intervention group (pre-pregnancy care): n=181 Control group: n=499

Other information	Not all women reported reading the relevant leaflet. The study reports that around 40% of women read it. Study did not adjust for confounders.

BMI: Body mass index; kg: kilograms; m: metres; UK: United Kingdom.

Study arms

Intervention group (pre-pregnancy care) (n = 181)

Control group (no pre-pregnancy care, historical cohort) (n = 499)

Outcomes

Folic acid uptake

Outcome	**Intervention group (pre-pregnancy care), n = 178**	**Control group (no pre-pregnancy care, historical cohort), n = 420**
5mg folic acid supplementation No of events	n = 157; % = 88.2	n = 112; % = 26.7

mg: milligram; n: number of participants.

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Moderate *(Only women who achieved pregnancy following pre-pregnancy care were included study which may overestimate the result)*
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Insufficient information to assess bias that may arise from missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious
Overall bias	Risk of bias variation across outcomes	N/A

Section	Question	Answer
Overall bias	Directness	Directly applicable

N/A: not applicable.

Schwarz, 2008

Bibliographic Reference	Schwarz, Eleanor Bimla; Sobota, Mindy; Gonzales, Ralph et al. Computerized counseling for folate knowledge and use: a randomized controlled trial; American journal of preventive medicine; 2008; vol. 35 (no. 6); 568-571

Study details

Country/ies where study was carried out	USA
Study type	Randomised controlled trial (RCT)
Study dates	March 2005 to July 2005
Inclusion criteria	• women aged 18-45 years
Exclusion criteria	Women who: • were unlikely to become pregnant in the next year because they were currently pregnant, had undergone a hysterectomy or tubal ligation, had an intrauterine device in place, had a partner who had undergone a vasectomy, or was aged >45 years

	• did not have a telephone • were relocating.
Patient characteristics	Not reported
Intervention(s)/control	**Intervention:** computerised counselling about periconception folate supplementation comprising: 1. A 15-minute computer module comprising video answers to 9 folate-related questions for participants to watch. 2. A bottle of 200 tablet of folate (400mcg) with written instructions suggesting the ingestion of one tablet daily. **Control:** computerised counselling about emergency contraception comprising: 1. A computer module on emergency contraception. 2. A sample of emergency contraception tablets.
Duration of follow-up	6 months
Sources of funding	Not industry funded
Sample size	N = 446
Other information	Although few women (4%) stated that they were trying to become pregnant, 14% reported that they wouldn't mind becoming pregnant. However, in the 6 months prior to enrolling, this group of women had experienced considerable risk for unintended pregnancy, as more than half reported one or more episodes of vaginal intercourse with a man without the use of any form of contraception. Study reports other measures of knowledge but only the most relevant that can be standardised across studies have been extracted and reported.

mcg: microgram; USA: United States of America.

Study arms

Intervention arm: computerised counselling on folate supplementation (n = 227)

Control arm: computerised counselling on emergency contraception (n = 219)

Outcomes

Change in Knowledge and use of folate supplement

Outcome	Intervention arm: computerised counselling on folate supplementation, n = 138	Control arm: computerised counselling on emergency contraception, n = 127
Learned that folate can prevent birth defects (n (%)) No of events	n = 63; % = 46	n = 24; % = 19
Learned that folate is most important in the very first weeks of pregnancy (n (%)) No of events	n = 57; % = 41	n = 20; % = 16
Started taking a folate supplement (n (%)) No of events	n = 50; % = 36	n = 28; % = 22

n: number of participants.

Learned that folate can prevent birth defects - Polarity - Higher values are better

Learned that folate is most important in the very first weeks of pregnancy - Polarity - Higher values are better

Started taking a folate supplement - Polarity - Higher values are better
This analysis includes only women who completed the follow up
Learned indicates a positive change in knowledge, meaning that a woman who did not know something at baseline knew the correct answer at follow-up. In this analysis, women who knew that folate can prevent birth defects or were using a supplement at baseline were presumed to have received no benefit from this intervention.

Critical appraisal - NGA Critical appraisal - Cochrane RoB 2.0 - standard RCT

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Some concerns about the absence of baseline characteristics)*
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 *(No serious concerns in this domain)*
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 *(No serious concerns in this domain)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low *(No serious concerns in this domain)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Self-reported outcomes)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Results may be selective as there is no reporting of baseline values to observe differences)*
Overall bias and Directness	Risk of bias judgement	Some concerns *(The study is judged to raise some concerns in at least one domain.)*
Overall bias and Directness	Overall Directness	Directly applicable
Overall bias and Directness	Risk of bias variation across outcomes	N/A

N/A: not applicable.

Tripathi, 2010

Bibliographic Reference	Tripathi, A; Rankin, J; Aarvold, J; Chandler, C; Bell, R; Tripathi, Avnish; Rankin, Judith; Aarvold, Joan; Chandler, Colin; Bell, Ruth; Preconception counseling in women with diabetes: a population-based study in the north of England.; Diabetes Care; 2010; vol. 33 (no. 3); 586-588

Study details

Country/ies where study was carried out	United Kingdom
Study type	Retrospective cohort study

Study dates	1 January 2001 to 31 December 2004
Inclusion criteria	• All singleton pregnancies delivered between 1 January 2001 and 31 December 2004
Exclusion criteria	Not reported
Patient characteristics	**Maternal age at delivery (Mean, SD), years** 29 (6.3) **Type 1 Diabetes, n (%)** 448 (77) **Primipara, n (%)** 208 (36) Characteristics not presented by groups
Intervention(s)/control	Intervention: Preconception counselling (no additional details provided) Control: No preconception counselling
Duration of follow-up	Not reported
Sources of funding	Not industry funded
Sample size	N = 588

Other information	Data was extracted from the Northern Diabetes in Pregnancy Survey (NorDIP) database maintained at the Regional Maternity Survey Office, Newcastle upon Tyne, UK. Data included information regarding periconceptual care, sociodemographic characteristics, and pregnancy outcome. Cases from 2002 were previously included in a national cohort study. Multivariate analysis was unclear for folic acid intake outcome. Therefore, nominal values (number and percentages) were extracted and used in analysis. Preconception folic acid uptake was used in analysis as there was no clear timepoint in the postconception uptake data. Study adjusted for type of diabetes, IMD score, ethnicity, age at delivery, and hospital of booking

IMD: index of multiple deprivation; n: number of participants; SD: standard deviation; UK: United Kingdom.

Study arms

Intervention arm: preconception counselling (n = 240)

Control arm: No preconception counselling (n = 297)

Outcomes

Study timepoints

- -3 month (3 months preconception)
- 0 month (Post conception)

Folic acid intake

Outcome	Intervention arm: preconception counselling, -3 month, n = 240	Intervention arm: preconception counselling, 0 month, n = 240	Control arm: No preconception counselling, -3 month, n = 297	Control arm: No preconception counselling, 0 month, n = 297
Folic acid intake 3 months preconception (n (%)) No of events	n = 134; % = 68.4	N/A	n = 62; % = 31.6	N/A

n: number of participants; N/A: not applicable.

Folic acid intake - Polarity - Higher values are better

Critical appraisal - NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Low

Section	Question	Answer
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(No information on missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Low
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

van Dijk, 2020

Bibliographic Reference	van Dijk, M.R.; Koster, M.P.H.; Oostingh, E.C.; Willemsen, S.P.; Steegers, E.A.P.; Steegers-Theunissen, R.P.M.; A mobile app lifestyle intervention to improve healthy nutrition in women before and during early pregnancy: Single-center randomized controlled trial; Journal of Medical Internet Research; 2020; vol. 22 (no. 5); e15773

Study details

Country/ies where study was carried out	The Netherlands
Study type	Randomised controlled trial (RCT)
Study dates	May 2014 to January 2017
Inclusion criteria	Women between aged 18 and 45 years • who were in possession of a smartphone with internet access • who resided in the Netherlands • were contemplating pregnancy or already pregnant (<13 weeks of pregnancy).
Exclusion criteria	Women who • had insufficient knowledge or understanding of the Dutch language • were being treated by a dietician to lose weight in the context of fertility treatment • were on a vegan diet.
Patient characteristics	**Age, median (IQR), years** Intervention group = 30.6 (5.3) Control group = 30.7 (5.7) **BMI, median (IQR), kg/m^2** Intervention group = 24.2 (6.0)

	Control group = 23.7 (5.4) **Pregnant at enrolment, n (%)** Intervention group = 36 (33) Control group = 37 (33.9)
Intervention(s)/control	Intervention: Full version of lifestyle change intervention including: • All functionality and personalised interaction involving tailored coaching, comprising a maximum of three emails or text messages per week, which contained seasonal recipes, incentives, feedback, recommendations, and additional questions regarding the participant's diet. Control: A modified version of the lifestyle change intervention with limited functionality and no personalised interaction
Duration of follow-up	12 weeks
Sources of funding	Not industry funded
Sample size	N = 218 Intervention group n = 109 Control group n = 109
Other information	Missing data were handled using the last-observation-carried-forward method.

BMI: Body mass index; IQR: interquartile range; kg: kilograms; m: metres; n: number of participants.

Study arms

Lifestyle change intervention (n = 109)

Control (n = 109)

Outcomes

Study timepoints

- baseline
- 24 week

Folic acid supplement use

Outcome	Lifestyle change intervention vs Control, 24 week vs Baseline, n2 = 109, n1 = 109
Folic acid supplement use Beta coefficient (95% CI)	0.094 (-0.077 to 0.259)

CI: confidence interval; n: number of participants; vs: versus.

The linear regression model includes adjustment for baseline Dietary Risk Score (DRS) and randomisation

Critical appraisal - NGA Critical appraisal - Cochrane RoB 2.0 - standard RCT

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)	Some concerns *(No blinding and no information on deviations from intervention, making it difficult to ascertain the effect of non-blinding)*
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	Some concerns *(No information on reasons for loss-to-follow up. Baseline characteristics were similar for those who completed the interventions and those lost to follow-up)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	High *(Self-reported outcomes and participants were not blinded to the intervention)*
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	High *(Serious concerns in one or more domains)*
Overall bias and Directness	Overall Directness	Directly applicable

Section	Question	Answer
Overall bias and Directness	Risk of bias variation across outcomes	N/A

N/A: not applicable.

Van Dijk, 2016

Bibliographic Reference	Van Dijk, Matthijs R; Huijgen, Nicole A; Willemsen, Sten P; Laven, Joop Se; Steegers, Eric Ap; Steegers-Theunissen, Regine Pm; Impact of an mHealth Platform for Pregnancy on Nutrition and Lifestyle of the Reproductive Population: A Survey.; JMIR mHealth and uHealth; 2016; vol. 4 (no. 2); e53

Study details

Country/ies where study was carried out	The Netherlands
Study type	Controlled Before-and-after study
Study dates	2012 to 2013
Inclusion criteria	• women and men contemplating pregnancy or pregnant couples living in Rotterdam, the Netherlands • visiting the Erasmus Medical Center (MC), University Medical Center, or midwifery practices in Rotterdam.
Exclusion criteria	Not reported
Patient characteristics	Women completed, n = 1003

	Women stopped, n = 522 **Age, median (IQR), years** Women completed = 31.2 (27.7 - 34.6) Women stopped = 31.5 (27.9 - 35.2) **Pregnant, n (%)** Women completed = 416 (41.48) Women stopped = 187 (35.9) **Body mass index, kg/m^2** Total group BMI, median (IQR): Women completed = 24.0 (21.3-27.6) Women stopped = 24.0 (21.7-27.0) Overweight (25 - 29.99 kg/m^2), median (IQR): Women completed = 27.1 (25.8-28.4) Women stopped = 26.7 (25.9-28.1)

	Obese (BMI 30-60 kg/m^2), median (IQR): Women completed = 32.9 (31.3-35.8) Women stopped = 32.7 (31.2-36.1) Overweight, n (%): Women completed = 266 (26.52) Women stopped = 139 (26.7) Obese, n (%): Women completed = 141 (14.06) Women stopped = 68 (13.0) **No folic acid intake, n (%)** Women completed = 150 (14.96) Women stopped = 72 (13.8)
Intervention(s)/control	Intervention: Smarter Pregnancy platform

	• 6 months of coaching on the most prevalent inadequate nutrition and lifestyle behaviours (such as, vegetable, fruit, and alcohol intake) or the most strongly demonstrated associations of behaviours with fertility and pregnancy course and outcome (such as, tobacco and folic acid supplement use).
Duration of follow-up	No follow-up
Sources of funding	Not industry funded
Sample size	N = 1525 (women only)
Other information	Outcomes were self-reported. For each nutrition and lifestyle behaviour, only individuals that scored inadequate at baseline were examined. Study reports various timepoints (6, 12, 18 and 24 weeks) but only 6 weeks data has been extracted and used in the analysis as it is the most representative among the timepoints reported of the time that folic acid will be expected to be taken by women. Study did not adjust for confounders.

BMI: Body mass index; IQR: interquartile range; kg: kilograms; m: metres; n: number of participants.

Outcomes

Study timepoints

- baseline
- 6 week

Folic acid supplement use

Outcome	Study, Baseline, n = 222	Study, 6 week, n = 222
All women (% (95% CI)) n=222 % (95% CI)	0	53.6 (46.8 - 60.3)
Pregnant women n=10 % (95% CI)	0	56.2 (2.3 - 98.6)
Overweight and obese n=111 % (95% CI)	0	57.5 (47.1 - 67.2)

CI: confidence interval; n: number of participants.

All women - Polarity - Higher values are better

Critical appraisal - Cochrane Effective Practice and Organisation of Care (EPOC) risk of bias tool

Section	Question	Answer
Random sequence generation	Was the allocation sequence adequately generated?	N/A
Allocation concealment	Was the allocation adequately concealed?	N/A
Baseline outcome measurements	Were baseline outcome measurements similar?	Yes

Section	Question	Answer
Baseline characteristics	Were baseline characteristics similar?	Yes
Incomplete outcome data	Were incomplete outcome data adequately addressed?	N/A
Knowledge of the allocated interventions	Was knowledge of the allocated interventions adequately prevented during the study?	Unclear
Protection against contamination	Was the study adequately protected against contamination?	N/A
Selective outcome reporting	Was the study free from selective outcome reporting?	Unclear *(Unclear why the estimate is % (95% CI))*
Other risks of bias	Was the study free from other risks of bias?	Unclear *(It is unclear if study adjusted for confounding; reported estimate is % (95% CI))*
Overall judgements of risk of bias and directness	Overall risk of bias	Moderate risk of bias
Overall judgements of risk of bias and directness	Overall directness	Directly applicable

CI: confidence interval; N/A: not applicable.

Watkins, 2004

Bibliographic Reference	Watkins M; Brustrom J; Schulman J; Effectiveness of a free folic acid supplement program in family planning clinics.; Birth Defects Res A Clin Mol Teratol; 2004; vol. 6; 403-7

Study details

Country/ies where study was carried out	USA
Study type	Prospective cohort study
Study dates	January 2000 to January 2001
Inclusion criteria	• women aged 18-45 years • visited one of the six study clinics (family planning clinics).
Patient characteristics	**Age, n (%), years** All participants: 18-35 = 956 (87.5) 36-45 = 132 (12.1) Participants engaged with intervention, n=165: 18-35 = 138 (83.6)

	36-45 = 27 (16.4) Pill intervention, n=68: 18-35 = 58 (85.3) 36-45 = 10 (14.7) Education only, n=24: 18-35 = 17 (70.8) 36-45 = 7 (29.2)
Intervention(s)/control	**Pill intervention:** folic acid supplements (400mcg) and educational material about folic acid **Education only intervention:** folic acid brochure designed for women not contemplating pregnancy Clinic staff delivered the interventions as previously described.
Duration of follow-up	1 year
Sources of funding	Not industry funded
Sample size	N = 165
Other information	Study included an additional intervention group (Cereal intervention: super-fortified cereal fortified with 400 mcg of folic acid per serving and educational material) which was not considered relevant to this review.

	Prior to evaluation, two of the three pill clinics and one of the two cereal clinics had been distributing folic acid supplements. The other clinics were either planning to start distributing supplements (one pill clinic; one cereal clinic) or had no plans do so (education-only clinic). Knowledge about folic acid was assessed using two multiple-choice questions: “What have you read, seen, or heard about folic acid?” and “When is the best time for a woman to take folic acid?” Participants were asked to mark all answers that applied. For a response to be counted as correct, the participant must have only responded “prevents birth defects” to the first question and “before she gets pregnant” to the second. Study adjusted for visit number, intervention type, age, race/ethnicity, and education. Knowledge about folic acid and smoking status were included as covariates for the outcome folic acid supplementation uptake

n: number of participants; mcg: microgram; USA: United States of America.

Study arms

Pill intervention (n = 68)

Folic acid supplements (400 mcg) and educational material about folic acid

Education only intervention (n = 24)

Educational material only

Outcomes

Folic acid knowledge

Outcome	Education only intervention vs Pill intervention, n1 = 24 , n2 = 68
Folic acid knowledge Odds ratio/95% CI	2.9 (1.12 to 7.49)
Folic acid consumption Multivariate analysis: Results for main effects model including visit number, intervention type, knowledge about folic acid, age, race/ethnicity, education, and smoking status as predictors. Odds ratio/95% CI	0.71 (0.33 to 1.52)

CI: confidence interval; mcg: microgram; n: number of participants; vs: versus.

Multivariate analysis: Results for main effects model including visit number, intervention type, knowledge about folic acid, age, race/ethnicity, education, and smoking status as predictors.

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Low
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Adherence to intended intervention unclear and no analysis to adjust for any deviations from intended treatment)*
5. Bias due to missing data	Risk of bias judgement for missing data	Low
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(Self-reported outcomes)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Moderate
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

Yamamoto, 2018

Bibliographic Reference	Yamamoto, J.M.; Hughes, D.J.F.; Evans, M.L.; Karunakaran, V.; Clark, J.D.A.; Morrish, N.J.; Rayman, G.A.; Winocour, P.H.; Hambling, C.; Harries, A.W.; Sampson, M.J.; Murphy, H.R.; Community-based pre-pregnancy care programme improves pregnancy preparation in women with pregestational diabetes; Diabetologia; 2018; vol. 61 (no. 7); 1528-1537

Study details

Country/ies where study was carried out	UK
Study type	Uncontrolled before-and-after study
Study dates	1 June 2013 to 28 February 2017
Inclusion criteria	• women diagnosed type 1 or type 2 diabetes and aged between 16 and 45 years • women attending primary care or antenatal diabetes clinics.
Exclusion criteria	• women who were pregnant, recently widowed, those who had had a hysterectomy, serious medical and/or psychological problems.
Patient characteristics	**Age (mean, SD) type 1 diabetes** Control group (Before pre-pregnancy care (PPC)) = 31.2 (5.9) Intervention group (After PPC) = 30.2 (5.8) **Age (mean, SD), type 2 diabetes** Control group (Before PPC) = 34.7 (5.2) Intervention group (After PPC) = 33.4 (5.4)

Intervention(s)/control	Intervention: pre-pregnancy care (PPC) program. It involved distributing printed and electronic copies of a pre-pregnancy care leaflet to primary care centres and specialist diabetes maternity clinics. Preconception care templates were embedded into the electronic healthcare records with alerts for healthcare professionals to promote its use during visits. Women were advised to take 5mg folic acid daily Control group: women before the pre-pregnancy care (PPC) program
Duration of follow-up	Not reported
Sources of funding	No industry funded
Sample size	Control group (Before PPC), n = 494 Intervention group (After PPC), n = 337
Other information	Study did not adjust for confounders

mg: milligram; SD: standard deviation; UK: United Kingdom.

Study arms

Control group: Before PPC (n = 494)

Intervention group: After PPC (n = 337)

Outcomes

Folic acid uptake

Outcome	Control group: Before PPC, n = 494	Intervention group: After PPC , n = 337
Folic acid uptake Any dose Sample size	n = 245; % = 49.5	n = 186; % = 55.2
Folic acid uptake - 5mg daily Sample size	n = 212; % = 42.9	n = 164; % = 48.6

mg: milligram; n: number of participants; PPC: pre-pregnancy care.

Folic acid uptake - Polarity - Higher values are better

Folic acid uptake - 5mg daily - Polarity - Higher values are better

Critical appraisal – NGA Critical appraisal – ROBINS-I

Section	Question	Answer
1. Bias due to confounding	Risk of bias judgement for confounding	Moderate *(No adjustment for confounding)*
2. Bias in selection of participants into the study	Risk of bias judgement for selection of participants into the study	Low
3. Bias in classification of interventions	Risk of bias judgement for classification of interventions	Low

Section	Question	Answer
4. Bias due to deviations from intended interventions	Risk of bias judgement for deviations from intended interventions	Moderate *(Not all participants completed the education intervention)*
5. Bias due to missing data	Risk of bias judgement for missing data	Moderate *(Some missing data reported and no evidence that the results were robust to the presence of missing data)*
6. Bias in measurement of outcomes	Risk of bias judgement for measurement of outcomes	Moderate *(No information on whether outcome assessors were aware of the intervention received)*
7. Bias in selection of the reported result	Risk of bias judgement for selection of the reported result	Low
Overall bias	Risk of bias judgement	Serious *(The study is judged to raise high risk of bias due to moderate concerns in 3 domains)*
Overall bias	Risk of bias variation across outcomes	N/A
Overall bias	Directness	Directly applicable

N/A: not applicable.

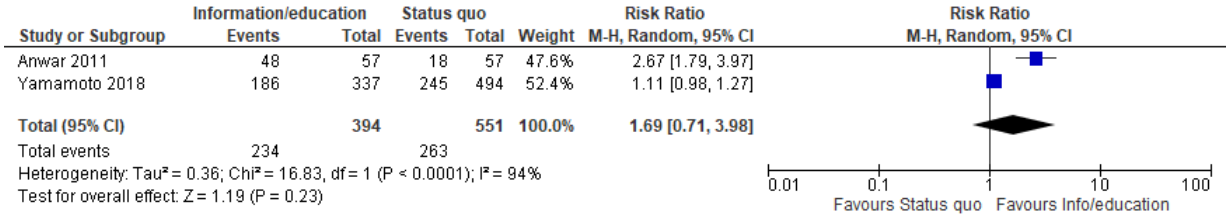
Appendix E Forest plots

Forest plots for review question: What interventions are effective to increase uptake of folic acid supplementation 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.

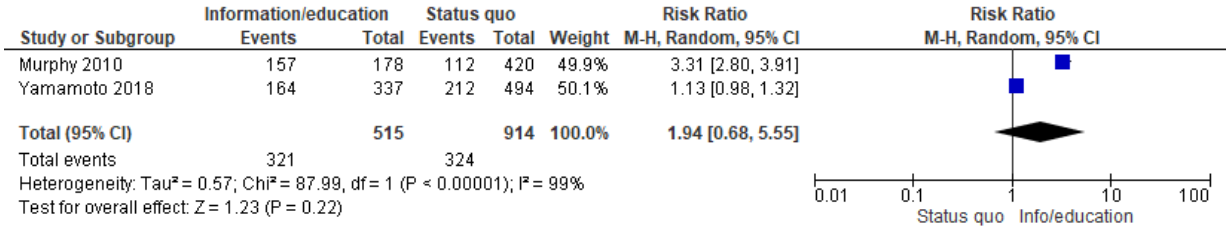
Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – combined components

Figure 2: Folic acid supplementation uptake (all doses) (follow-up 8 weeks or not reported)



CI: confidence interval; df: degrees of freedom; Info: information; M-H: Mantel-Haenszel.

Figure 3: 5mg folic acid supplementation uptake (follow-up at 3 months or not reported)

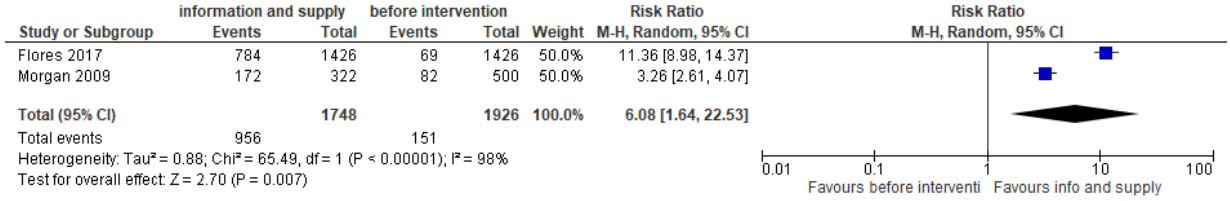


CI: confidence interval; df: degrees of freedom; Info: information; M-H: Mantel-Haenszel

Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI

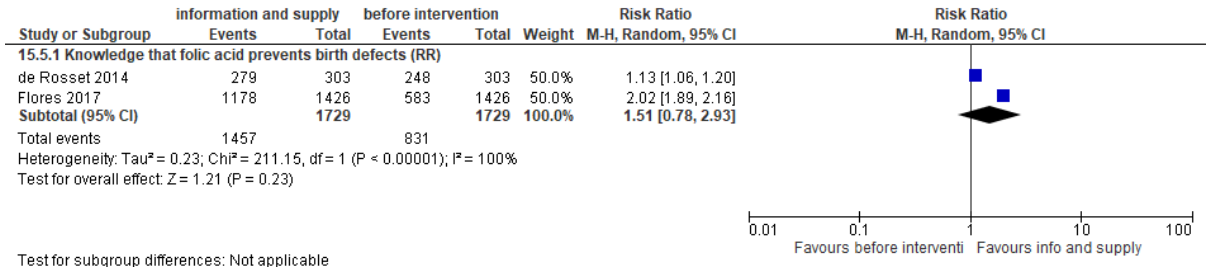
thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Figure 4: Folic acid supplementation uptake (all doses) (follow-up at 4 to 10 months)



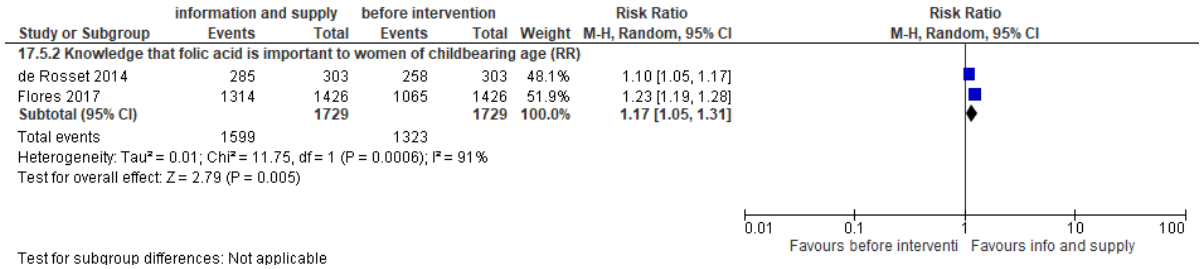
CI: confidence interval; df: degrees of freedom; Info: information; M-H: Mantel-Haenszel.

Figure 5: Change in knowledge: knowledge that folic acid prevents birth defects (What have you read, seen or heard about folic acid? Only reporting for those that answered 'it prevents birth defects') (follow-up at 4 months)



CI: confidence interval; df: degrees of freedom; Info: information; M-H: Mantel-Haenszel.

Figure 6: Change in knowledge: knowledge that folic acid is important to women of childbearing age (Which vitamins or mineral supplements do you think are important to women of childbearing age? Only reports those that answered folic acid) (follow-up at 4 months)



CI: confidence interval; df: degrees of freedom; Info: information; M-H: Mantel-Haenszel.

Appendix F GRADE tables

GRADE tables for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Table 6: Evidence profile for Comparison 1: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with BMI thresholds in the overweight or obese range (Mixed strata for folic acid supplementation dose, age, deprived socioeconomic group and comorbidities) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses) (follow-up 6 weeks). Components of intervention (digital/electronic and textual intervention, delivered preconception and during pregnancy, aimed at individuals, on demand tailored intervention, delivered by folic acid supplementation champion (researchers), using mobile platform, and transtheoretical model, social cognitive theory and Fogg's behavioural model)												
1 (van Dijk 2016)	controlled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	NR	NR	% 57.5 (47.1 to 67.2)[3,4]	-	VERY LOW	CRITICAL

BMI: Body mass index; CI: confidence interval; NR: not reported
[1] Serious risk of bias in the evidence contributing to the outcomes as per EPOC Risk of bias tool.
[2] Sample size <200 (sample size used because imprecision could not be assessed using default minimally important differences).
[3] This result was folic acid uptake after the intervention at 6 weeks. No information was reported on uptake at baseline. Data for folic acid supplementation uptake was reported for n=222 women out of total women included (N=1525). For overweight and obese category, n = 111.
[4] Clinical importance could not be assessed for this outcome as paper does not provide information to assess changes from baseline.

Table 7: Evidence profile for Comparison 2: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women without comorbidities (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses) (follow-up 6 weeks). Components of intervention (digital/electronic and textual intervention, delivered preconception and during pregnancy, aimed at individuals, on demand tailored intervention, delivered by folic acid supplementation champion (researchers), using mobile platform, and transtheoretical model, social cognitive theory and Fogg's behavioural model)												
1 (van Dijk 2016)	controlled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	NR	NR	% 53.6 (46.8 to 60.3)[3]	-	VERY LOW	CRITICAL

aOR: adjusted odds ratio; BMI: Body mass index; CI: confidence interval; NR: not reported
[1] Serious risk of bias in the evidence contributing to the outcomes as per EPOC Risk of bias tool.
[2] Sample size between 200 and 400 (sample size used because imprecision could not be assessed using default minimally important differences).
[3] This result was folic acid uptake after the intervention at 6 weeks. No information was reported on uptake at baseline. Reported for n=222 women out of total women included (N=1525). Clinical importance could not be assessed for this outcome as paper does not provide information to assess changes from baseline.

Table 8: Evidence profile for Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses). (follow-up at 5 months). Components of intervention (visual interventions, delivered preconception, aimed at individuals, general intervention, delivered by healthcare practitioner, health or social care worker (not specified, DVD created by combined user and multi-professional advisory group), DVD distributed by health professionals but watched in individuals' on time/place and using expanded health belief model)												
1 (Holmes 2017)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	46/57 (80.7%)	47/111 (42.3%)	aOR 4.85 (1,94 to 12.11)	357 more per 1000 (from 164 more to 475 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
5mg folic acid supplementation uptake. (follow-up at 5 months). Components of intervention (visual interventions, delivered preconception, aimed at individuals, general intervention, delivered by healthcare practitioner, health or social care worker (not specified, DVD created by combined user and multi-professional advisory group), DVD distributed by health professionals but watched in individuals' on time/place and using expanded health belief model)												
1 (Holmes 2017)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38/41 (92.7%)	21/28 (75%)	aOR 6.39 (0.93 to 44.07)	200 more per 1000 (from 14 fewer to 242 more)	VERY LOW	CRITICAL **POSS. IMP. BENEFIT**
Folic acid supplementation uptake (all doses). (follow-up post conception). Components of the intervention (Printed interventions, other components not reported)												
1 (Tripathi 2010)	retrospective cohort studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	134/240 (55.8%)	62/297 (20.9%)	RR 2.67 (2.09 to 3.43)	349 more per 1000 (from 228 more to 508 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (all doses) (follow-up 8 weeks or not reported)*												
2[2]	uncontrolled before-and-after studies	very serious[3]	very serious[4]	no serious indirectness	serious[5]	none	234/394 (59.4%)	263/551 (47.7%)	RR 1.69 (0.71 to 3.98)	115 more per 1000 (from 48	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
										fewer to 196 more)		**NO EV. OF IMP. DIFF.**
5mg folic acid supplementation uptake (follow-up at 3 months or not reported)*												
2[6]	uncontrolled before-and-after studies	very serious[3]	very serious[4]	no serious indirectness	very serious[7]	none	321/515 (62.3%)	324/914 (35.4%)	RR 1.94 (0.68 to 5.55)	333 more per 1000 (from 113 fewer to 1000 more)	VERY LOW	CRITICAL **NO EV. OF IMP. DIFF.**

aOR: adjusted Odds Ratio; BMI: body Mass Index; CI: confidence Interval; DVD: digital versatile disc; NR: not reported; OR: odds ratio; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] Anwar 2011, Yamamoto 2018.
[3] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[4] Very serious heterogeneity unexplained by subgroup analysis (I^2=94% for corresponding folic acid supplementation uptake (all doses), I^2=99% for corresponding 5mg folic acid supplementation uptake)
[5] 95% CI crosses 1 MID (0.8 or 1.25).
[6] Murphy 2010, Yamamoto 2018
[7] 95% CI crosses 2 MIDs (0.8 and 1.25)
** Components of the intervention for Yamamoto 2018 (Printed and digital/electronic intervention, delivered during the preconception period, aimed at individuals, general intervention, delivered by healthcare practitioner, health or social care worker (specialist antenatal diabetes team), during consultation with healthcare professional or health and social worker, no theories mentioned); for Anwar 2011 (Face-to-face intervention, delivered during the preconception period, aimed at individuals, on demand tailored intervention, delivered by healthcare practitioner, health or social care worker (consultant obstetrician, consultant physician, diabetes specialist nurse and a dietician), in specialist clinics, no theories mentioned); for Murphy 2010 (Face to face intervention, delivered during the preconception period, aimed at individuals, general intervention, delivered by healthcare practitioner, health or social care worker (diabetes physician, specialist nurse, midwife, or obstetrician), in specialist clinics, no theory mentioned)*

The following GRADE tables (Table 9 to 12) are sensitivity analyses for Comparison 3: intervention group 1 with intervention components: mode of delivery, when the intervention is delivered, individualised or targeted interventions, who delivers the intervention, where the intervention is delivered, behaviour change models, theories or techniques. Sensitivity analysis was not carried

out for components 2, 3 and 7 as there was insufficient information from one study and in the other 2 studies the components were the same for the same outcome.

Table 9: Evidence profile for Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – Sensitivity analysis for components 1: mode of delivery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses) (follow-up 8 weeks). Component of the intervention (Face to face interventions)												
1 (Anwar 2011)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/57 (84.2%)	18/57 (31.6%)	RR 2.67 (1.79 to 3.97)	527 more per 1000 (from 249 more to 938 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (all doses) (follow-up not reported). Component of the intervention (Printed and digital/electronic intervention)												
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	186/337 (55.2%)	245/494 (49.6%)	RR 1.11 (0.98 to 1.27)	55 more per 1000 (from 10 fewer to 134 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**
5mg folic acid supplementation uptake (follow-up at 3 months). Components of the intervention (face to face intervention)												
1 (Murphy 2010)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/178 (88.2%)	112/420 (26.7%)	RR 3.31 (2.8 to 3.91)	616 more per 1000 (from 480 more to 776 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
5mg folic acid supplementation uptake (follow-up not reported). Components of the intervention (Printed and digital/electronic intervention)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	164/337 (48.7%)	212/494 (42.9%)	RR 1.13 (0.98 to 1.32)	56 more per 1000 (from 9 fewer to 137 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**

BMI: Body mass index; CI: confidence interval; NR: not reported; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool
[3] 95% CI crosses 1 MID (0.8 or 1.25)

Table 10: Evidence profile for Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – Sensitivity analysis for component 4: on demand individualised/tailored interventions or general interventions*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Interventions using information/education provision	Status quo (including no treatment)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses) (follow-up 8 weeks). Component of the intervention (on demand, tailored interventions based on needs)												
1 (Anwar 2011)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/57 (84.2%)	18/57 (31.6%)	RR 2.67 (1.79 to 3.97)	527 more per 1000 (from 249 more to 938 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (all doses) (follow-up not reported). Component of the intervention (general, aimed at population of interest)												

1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	186/337 (55.2%)	245/494 (49.6%)	RR 1.11 (0.98 to 1.27)	55 more per 1000 (from 10 fewer to 134 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[3] 95% CI crosses 1 MID (0.8 or 1.25)
**Sensitivity analysis was not carried out for component 4 of the intervention for the outcome 5mg folic acid supplementation as the component (general intervention, aimed at the population of interest) is the same in both studies (Anwar 2011 and Yamamoto 2018).*

Table 11: Evidence profile for Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – Sensitivity analysis for component 5: who delivers the intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventions using information/education provision**	**Status quo (including no treatment)**	**Relative (95% CI)**	**Absolute**		
Folic acid supplementation uptake (all doses) (follow-up 8 weeks). Component of the intervention (healthcare practitioner, health or social care worker (consultant obstetrician, consultant physician, diabetes specialist nurse and a dietician))												
1 (Anwar 2011)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/57 (84.2%)	18/57 (31.6%)	RR 2.67 (1.79 to 3.97)	527 more per 1000 (from 249 more to 938 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (follow-up not reported). Component of the intervention (healthcare practitioner, health or social care worker (specialist antenatal diabetes team))												
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	186/337 (55.2%)	245/494 (49.6%)	RR 1.11 (0.98 to 1.27)	55 more per 1000 (from 10 fewer to 134 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**

5mg folic acid supplementation uptake (follow-up at 3 months). Components of the intervention (delivered by healthcare practitioner, health or social care worker (diabetes physician, specialist nurse, midwife, or obstetrician))												
1 (Murphy 2010)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/178 (88.2%)	112/420 (26.7%)	RR 3.31 (2.8 to 3.91)	616 more per 1000 (from 480 more to 776 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
5mg folic acid supplementation uptake (follow-up not reported). Components of the intervention (healthcare practitioner, health or social care worker (specialist antenatal diabetes team))												
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	164/337 (48.7%)	212/494 (42.9%)	RR 1.13 (0.98 to 1.32)	56 more per 1000 (from 9 fewer to 137 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[3] 95% CI crosses 1 MID (0.8 or 1.25)

Table 12: Evidence profile for Comparison 3: Intervention group 1: Interventions using information/education provision versus status quo (including no treatment) in women with comorbidities (diabetes) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group) – Sensitivity analysis for component 6: where the intervention is delivered

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventions using information/education provision**	**Status quo (including no treatment)**	**Relative (95% CI)**	**Absolute**		
Folic acid supplementation uptake (all doses) (follow-up not reported). Component of the intervention (during consultation with healthcare professionals or health and social care worker)												
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	186/337 (55.2%)	245/494 (49.6%)	RR 1.11 (0.98 to 1.27)	55 more per 1000 (from 10 fewer to 134 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**
Folic acid supplementation uptake (all doses) (follow-up 8 weeks). Component of the intervention (in specialist clinics)												

1 (Anwar 2011)	uncontrolled before-and-after study	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	48/57 (84.2%)	18/57 (31.6%)	RR 2.67 (1.79 to 3.97)	527 more per 1000 (from 249 more to 938 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
5mg folic acid supplementation uptake (follow-up not reported).. Components of the intervention (during consultation with healthcare professional or health and social worker)												
1 (Yamamoto 2018)	uncontrolled before-and-after study	very serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	164/337 (48.7%)	212/494 (42.9%)	RR 1.13 (0.98 to 1.32)	56 more per 1000 (from 9 fewer to 137 more)	VERY LOW	CRITICAL **NO IMP. DIFF.**
5mg folic acid supplementation uptake (follow-up at 3 months). Components of the intervention (in specialist clinics)												
1 (Murphy 2010)	uncontrolled before-and-after study	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	157/178 (88.2%)	112/420 (26.7%)	RR 3.31 (2.8 to 3.91)	616 more per 1000 (from 480 more to 776 more)	VERY LOW	CRITICAL **IMP. BENEFIT**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] 95% CI crosses 1 MID (0.8 or 1.25)
[3] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.

Table 13: Evidence profile for Comparison 4: Intervention group 1: Focused interventions using information/education provision versus limited information/education provision (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventions using focused information/education provision**	**Limited information/education provision**	**Relative (95% CI)**	**Absolute**		
Folic acid supplementation (follow-up at end of first trimester). Components of the intervention (face to face and printed interventions, delivered during the first 12 weeks of pregnancy, group based, general intervention, delivered by specially trained staff including medical assistants, midwives and gynaecologists, setting: NR, no theory mentioned												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Interventions using focused information/education provision**	**Limited information/education provision**	**Relative (95% CI)**	**Absolute**		
1 (Geyer 2022)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[3]	none	5[4]	5[4]	aOR 1.1 (0.92 to 1.31)[5]	21 more per 1000 (from 18 fewer to 61 more)	VERY LOW	CRITICAL **NO EV. OF IMP. DIFF.**
Folic acid supplementation uptake (follow-up at 6 weeks post-conception). Components of the intervention (digital/electronic and printed interventions, delivered during the preconception period and during pregnancy, aimed at individuals, tailored interventions, delivered by researchers/health professionals, on mobile phones, based on unspecified models of behaviour change												
1 (Van Dijk 2020)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[6]	none	NR	NR	beta 0.094 (-0.077 to 0.259)[7]	-	VERY LOW	CRITICAL **NO EV. OF IMP. DIFF.**

aOR: adjusted odds ratio; BMI: Body mass index; CI: confidence interval; NR: not reported; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per RoB 2.
[2] Intervention is indirect due to the primary aim being to decrease the proportion of women who gained excessive weight during pregnancy.
[3] 95% CI crosses 1 MID (0.8 or 1.25).
[4] Unit of randomisation numbers provided as cluster RCT. Individual N were 1052 for intervention and 1039 for comparator.
[5] Analysis adjusted for pre-pregnancy BMI category, age, educational level, and parity.
[6] Sample size <200.
[7] Clinical importance based on statistical significance as provided in the paper

Table 14: Evidence profile for Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses), measured by serum folate (nmol/L) (Better indicated by higher values). (follow-up at 4 months) Components of the intervention (face to face interventions, delivered during the preconception period, aimed at individuals, general Intervention, who delivered the intervention: NR, where intervention was delivered: NR and no theory mentioned)												
1 (de Weerd 2002)	uncontrolled before-and-after study	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	52	52	-	MD 2.10 higher (2.41 lower to 6.61 higher)	VERY LOW	CRITICAL **NO EV. OF IMP. DIFF.**
Folic acid supplementation uptake (all doses) (follow-up at 4 to 10 months)*												
2[3]	uncontrolled before-and-after studies	very serious[4]	very serious[5]	no serious indirectness	no serious imprecision	none	956/1748 (54.7%)	151/1926 (7.8%)	RR 6.08 (1.64 to 22.53)	440 more per 1000 (from 310 more to 570 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Change in knowledge: Knowledge that folic acid prevents birth defects (What have you read, seen or heard about folic acid? Only reporting for those that answered 'it prevents birth defects') (follow-up at 4 months)*												
2[6]	uncontrolled before-and-after studies	very serious[4]	very serious[5]	no serious indirectness	very serious[7]	none	1457/1729 (84.3%)	831/1729 (48.1%)	RR 1.51 (0.78 to 2.93)	260 more per 1000 (from 60 less to 580 more)	VERY LOW	IMPORTANT **NO EV. OF IMP. DIFF.**
Change in knowledge: Knowledge that folic acid is important to women of childbearing age (Which vitamins or mineral supplements do you think are important to women of childbearing age? Only reports those that answered folic acid) (follow-up at 4 months)*												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
2[6]	uncontrolled before-and-after studies	very serious[4]	very serious[5]	no serious indirectness	serious[8]	none	1599/1729 (92.5%)	1323/1729 (76.5%)	RR 1.17 (1.05 to 1.31)	130 more per 1000 (from 50 more to 220 more)	VERY LOW	IMPORTANT NO EV. OF IMP. DIFF.
Change in knowledge: Knowledge of the correct time to use folic acid (When should a woman take folic acid? Only reporting for those that answered 'before she gets pregnant'). (follow-up at 4 months) Components of the intervention (face to face and digital/electronic (telephone) interventions, delivered preconception, aimed at groups, general intervention, delivered by folic acid supplementation 'champion' (promotora), where the intervention was delivered: NR and no theories mentioned)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	401/1426 (28.1%)	458/1426 (32.1%)	RR 0.88 (0.78 to 0.98)	39 fewer per 1000 (from 6 fewer to 71 fewer)	VERY LOW	IMPORTANT NO EV. OF IMP. DIFF.

BMI: Body mass index; CI: confidence interval; MD: mean difference; NR: not reported; RR: risk ratio; SE: standard error
[1] Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] 95% CI crosses 1 MID (0.5 x control group SD, for 'Folic acid supplementation uptake - measured by serum folate' = -4.69, +4.69).
[3] Flores 2017, Morgan 2009.
[4] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[5] Very serious heterogeneity unexplained by subgroup analysis (I2=98% for corresponding folic acid supplementation uptake analysis; I2=100% for corresponding change in knowledge: knowledge that folic acid prevents birth defects analysis I2=91% for corresponding change in knowledge: knowledge that folic acid is important to women of childbearing age analysis). No sufficient information for subgroup analysis. Random effects analysis used.
[6] deRosset 2014, Flores 2017.
[7] 95% CI crosses 2 MIDs (0.8 and 1.25).
[8] 95% CI crosses 1 MID (0.8 or 1.25).
** Components of the intervention for deRosset 2014 (Face to face and printed interventions, delivered preconception, aimed at groups, general intervention, delivered by folic acid supplementation 'champion' (promotora), delivered at recruitment site such as community venues, churches etc or other venues, no theories mentioned); Flores 2017 (Face to face and digital/electronic (telephone) interventions, delivered preconception, aimed at groups, general intervention, delivered by folic acid supplementation 'champion' (promotora), where the intervention was delivered: NR and no theories mentioned); Morgan 2009 (Face to face and printed interventions, delivered preconception, aimed at groups, general*

intervention, delivered by healthcare practitioner, health or social care worker (nurse), during consultation, no theories mentioned)

The following GRADE tables (Table 15 to Table 18) are sensitivity analysis for Comparison 5: Intervention group 5 with intervention components: mode of delivery, interventions aimed at individuals or groups, who delivers the intervention, where the intervention is delivered. Sensitivity analyses was not conducted for components 2, 4 and 7 as the components were the same across the pooled studies for the same outcome.

Table 15: Evidence profile for Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – Sensitivity analysis for component 1: mode of delivery

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (all doses, follow-up at 8 to 10 months). Components of the intervention (face to face and printed interventions)												
1 (Morgan 2009)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/322 (53.4%)	82/500 (16.4%)	RR 3.26 (2.61 to 4.07)	371 more per 1000 (from 264 more to 503 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (all doses, follow-up at 4 months). Components of the intervention (face to face and digital/electronic (telephone) interventions)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/1426 (55%)	69/1426 (4.8%)	RR 11.36 (8.98 to 14.37)	501 more per 1000 (from 386 more to 647 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Change in knowledge: Knowledge that folic acid prevents birth defects (follow-up at 4 months). Components of the intervention (face to face and printed interventions)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Multicomponent interventions (information/education provision and folic acid supply)**	**Control (before interventions)**	**Relative (95% CI)**	**Absolute**		
1 (deRosset 2014)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	279/303 (92.1%)	248/303 (81.8%)	RR 1.12 (1.06 to 1.2)	98 more per 1000 (from 49 more to 164 more)	VERY LOW	IMPORTANT **NO IMP. DIFF.**
Change in knowledge: Knowledge that folic acid is important to women of childbearing age (follow-up at 4 months). Components of the intervention (face to face and printed interventions)												
1 (deRosset 2014)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285/303 (94.1%)	258/303 (85.1%)	RR 1.1 (1.05 to 1.17)	85 more per 1000 (from 43 more to 145 more)	VERY LOW	IMPORTANT **NO IMP. DIFF.**
Change in knowledge: Knowledge that folic acid prevents birth defects (follow-up at 4 months). Components of the intervention (face to face and digital/electronic (telephone) interventions)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1178/1426 (82.6%)	583/1426 (40.9%)	RR 2.02 (1.89 to 2.16)	417 more per 1000 (from 364 more to 474 more)	VERY LOW	IMPORTANT **IMP. BENEFIT**
Change in knowledge: Knowledge that folic acid is important to women of childbearing age (follow-up at 4 months). Components of the intervention (face to face and digital/electronic (telephone) interventions)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1314/1426 (92.1%)	1065/1426 (74.7%)	RR 1.23 (1.19 to 1.28)	172 more per 1000 (from 142 more to 209 more)	VERY LOW	IMPORTANT **NO EV. OF IMP. DIFF.**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2] 95% CI crosses 1 MID (0.8 or 1.25).

Table 16: Evidence profile for Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – Sensitivity analysis for component 3: interventions aimed at individuals or groups*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (follow-up at 8 to 10 months). Components of the intervention (intervention aimed at individuals)												
1 (Morgan 2009)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/322 (53.4%)	82/500 (16.4%)	RR 3.26 (2.61 to 4.07)	371 more per 1000 (from 264 more to 503 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (follow-up at 4 months). Components of the intervention (intervention aimed at groups)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/1426 (55%)	69/1426 (4.8%)	RR 11.36 (8.98 to 14.37)	501 more per 1000 (from 386 more to 647 more)	VERY LOW	CRITICAL **IMP. BENEFIT**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
** Sensitivity analysis was not carried out for component 3 of the intervention for the outcomes Change in knowledge: Knowledge that folic acid prevents birth defects and Change in knowledge: Knowledge that folic acid is important to women of childbearing age as the component (intervention aimed at groups) are the same in both studies (deRosset 2014 and Flores 2017).*

Table 17: Evidence profile for Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – Sensitivity analysis for component 5: who delivers the intervention*

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (follow-up at 8 to 10 months). Components of the intervention (healthcare practitioner, health or social care worker (nurse))												
1 (Morgan 2009)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/322 (53.4%)	82/500 (16.4%)	RR 3.26 (2.61 to 4.07)	371 more per 1000 (from 264 more to 503 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (follow-up at 4 months). Components of the intervention (folic acid supplementation 'champion' (promotora))												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/1426 (55%)	69/1426 (4.8%)	RR 11.36 (8.98 to 14.37)	501 more per 1000 (from 386 more to 647 more)	VERY LOW	CRITICAL **IMP. BENEFIT**

BMI: Body mass index; CI: confidence interval; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
** Sensitivity analysis was not carried out for component 5 of the intervention for the outcomes Change in knowledge: Knowledge that folic acid prevents birth defects and Change in knowledge: Knowledge that folic acid is important to women of childbearing age as the component (folic acid supplementation 'champion' - promotora) are the same across pooled studies (deRosset 2014 and Flores 2017).*

Table 18: Evidence profile for Comparison 5: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus control (before interventions) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – Sensitivity analysis for component 6: where the intervention is delivered

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (follow-up at 8 to 10 months). Components of the intervention (During consultation with healthcare professionals or health and social care workers)												
1 (Morgan 2009)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/322 (53.4%)	82/500 (16.4%)	RR 3.26 (2.61 to 4.07)	371 more per 1000 (from 264 more to 503 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Folic acid supplementation uptake (follow-up at 4 months). Components of the intervention (Where intervention was delivered, NR)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/1426 (55%)	69/1426 (4.8%)	RR 11.36 (8.98 to 14.37)	501 more per 1000 (from 386 more to 647 more)	VERY LOW	CRITICAL **IMP. BENEFIT**
Change in knowledge: Knowledge that folic acid prevents birth defects (follow-up at 4 months). Components of the intervention (other (at recruitment site such as community venues, churches etc or other venues))												
1 (deRosset 2014)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	279/303 (92.1%)	248/303 (81.8%)	RR 1.12 (1.06 to 1.2)	98 more per 1000 (from 49 more to 164 more)	VERY LOW	IMPORTANT **NO IMP. DIFF.**
Change in knowledge: Knowledge that folic acid prevents birth defects (follow-up at 4 months). Components of the intervention (where the intervention was delivered, NR)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and folic acid supply)	Control (before interventions)	Relative (95% CI)	Absolute		
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1178/1426 (82.6%)	583/1426 (40.9%)	RR 2.02 (1.89 to 2.16)	417 more per 1000 (from 364 more to 474 more)	VERY LOW	IMPORTANT **IMP. BENEFIT**
Change in knowledge: Knowledge that folic acid is important to women of childbearing age (follow-up at 4 months). Components of the intervention (other (at recruitment site such as community venues, churches etc or other venues)												
1 (deRosset 2014)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	285/303 (94.1%)	258/303 (85.1%)	RR 1.10 (1.05 to 1.17)	85 more per 1000 (from 43 more to 145 more)	VERY LOW	IMPORTANT **NO IMP. DIFF.**
Change in knowledge: Knowledge that folic acid is important to women of childbearing age (follow-up at 4 months). Components of the intervention (where the intervention was delivered: NR)												
1 (Flores 2017)	uncontrolled before-and-after study	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1314/1426 (92.1%)	1065/1426 (74.7%)	RR 1.23 (1.19 to 1.28)	172 more per 1000 (from 142 more to 209 more)	VERY LOW	IMPORTANT **NO EV. OF IMP. DIFF.**

BMI: Body mass index; CI: confidence interval; NR: not reported; RR: risk ratio
[1] Very serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I risk of bias tool.
[2]95% CI crosses 1 MID (0.8 or 1.25).

Table 19: Evidence profile for Comparison 6: Intervention group 5: Multicomponent interventions (focused information/education provision and folic acid supply) versus control (unfocused information/education provision and folic acid supply) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (focused information/education provision and folic acid supply)	Control (unfocused information/education provision and folic acid supply)	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (follow-up at 6 months). Components of the intervention (face to face and printed intervention, delivered preconception, aimed at individuals, on demand tailored interventions, delivered by clinicians, during consultation and no theory mentioned)												
1 (Chilukuri 2018)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	71/163 (43.6%)	79/189 (41.8%)	aOR 2.04 (1.05 to 3.98)[3]	176 more per 1000 (from 12 more to 323 more)	LOW	CRITICAL **IMP. BENEFIT**

aOR: adjusted odds ratio; BMI: Body mass index; CI: confidence Interval; OR: odds ratio
[1] Serious risk of bias in the evidence contributing to the outcomes as per RoB 2.
[2] 95% CI crosses 1 MID (0.8 or 1.25).
[3] Analysis adjusted for age of the mother, age of the child, race/ethnicity, education, income, parity, and intention to have a pregnancy in the next 6 months.

Table 20: Evidence profile for Comparison 7: Intervention group 5: Multicomponent interventions (folic acid information/education provision and folic acid supply) versus multicomponent intervention control (emergency contraception (EC) information/education provision and EC supply) (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (FA information/education provision and FA supply)	Multicomponent intervention (Emergency contraception (EC) information/education provision and EC supply)	Relative (95% CI)	Absolute		

Folic acid supplementation uptake (follow-up at 6 months). Components of the intervention (visual intervention, interventions delivered during the preconception period, aimed at individuals, general interventions, delivered by video doctor, during consultation												
1 (Schwarz 2008)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	50/138 (36.2%)	28/127 (22%)	RR 1.64 (1.11 to 2.44)	141 more per 1000 (from 24 more to 317 more)	LOW	CRITICAL **IMP. BENEFIT**
Change in knowledge (follow-up at 6 months. Components of the intervention (visual intervention, interventions delivered during the preconception period, aimed at individuals, general interventions, delivered by video doctor, during consultation)												
1 (Schwarz 2008)	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	120/276 (43.5%)	44/254 (17.3%)	RR 2.51 (1.86 to 3.39)	262 more per 1000 (from 149 more to 414 more)	MODERATE	IMPORTANT **IMP. BENEFIT**
Change in knowledge: knowledge that folate can prevent birth defects (follow-up at 6 months). Components of the intervention (visual intervention, interventions delivered during the preconception period, aimed at individuals, general interventions, delivered by video doctor, during consultation												
1 (Schwarz 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	63/138 (45.7%)	24/127 (18.9%)	RR 2.42 (1.61 to 3.62)	268 more per 1000 (from 115 more to 495 more)	MODERATE	IMPORTANT **IMP. BENEFIT**
Change in knowledge: knowledge that folate is most important in the very first weeks of pregnancy (follow-up at 6 months). Components of the intervention (visual intervention, interventions delivered during the preconception period, aimed at individuals, general interventions, delivered by video doctor, during consultation												
1 (Schwarz 2008)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	57/138 (41.3%)	20/127 (15.7%)	RR 2.62 (1.67 to 4.11)	255 more per 1000 (from 106 more to 490 more)	MODERATE	IMPORTANT **IMP. BENEFIT**

BMI: Body mass index; CI: confidence Interval; FA: folic acid; RR: risk ratio

[1] *Serious risk of bias in the evidence contributing to the outcomes as per RoB 2.*
[2] *95% CI crosses 1 MID (0.8 or 1.25).*

Table 21: Evidence profile for Comparison 8: Intervention group 5: Multicomponent interventions (information/education provision and folic acid supply) versus information/education provision only (Mixed strata for folic acid supplementation dose, BMI thresholds, age, deprived socioeconomic group and comorbidities) – combined components

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Multicomponent interventions (information/education provision and FA supply)	Information/education provision only	Relative (95% CI)	Absolute		
Folic acid supplementation uptake (follow-up at 1 year). Components of the intervention (face to face and printed interventions, interventions delivered during the preconception period, aimed at individuals, general intervention, delivered by clinic staff, in family planning clinics												
1 (Watkins 2004)	prospective cohort study	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/68 (44.1%)	13/24 (54.2%)	aOR 0.71 (0.33 to 1.52)[3]	85 fewer per 1000 (from 261 fewer to 101 more)	VERY LOW	CRITICAL **NO EV. OF IMP. DIFF.**
Folic acid knowledge (Answered one or two questions correctly versus did not answer any questions correctly) (follow-up at 1 year). Components of the intervention (face to face and printed interventions, interventions delivered during the preconception period, aimed at individuals, general intervention, delivered by clinic staff, in family planning clinics												
1 (Watkins 2004)	prospective cohort study	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	NR	NR	aOR 2.9 (1.12 to 7.49)[5]	-	LOW	IMPORTANT **IMP. BENEFIT**

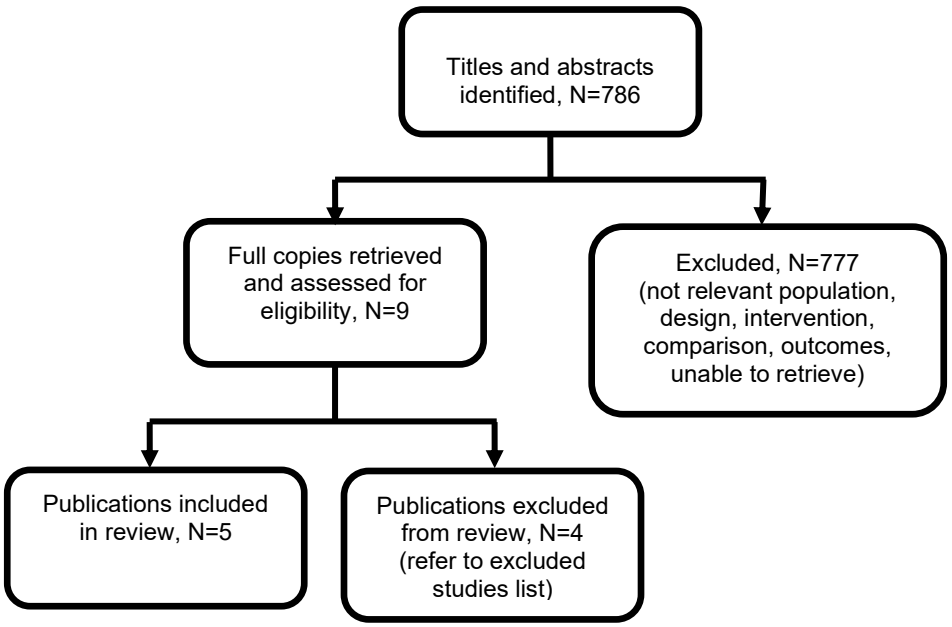
aOR: adjusted odds ratio; BMI: Body mass index; CI: confidence Interval; NR: not reported; OR: odds ratio
[1] *Serious risk of bias in the evidence contributing to the outcomes as per ROBINS-I.*
[2] *95% CI crosses 2 MIDs (0.8 and 1.25).*
[3] *Analysis adjusted for visit number, intervention type, knowledge about folic acid, age, race/ethnicity, education, and smoking status.*
[4] *95% CI crosses 1 MID (0.8 or 1.25).*
[5] *Analysis adjusted for visit number, intervention type, age, race/ethnicity, and education.*

Appendix G Economic evidence study selection

Study selection for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Figure shows the flow diagram of the selection process for economic evaluations of interventions aiming to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy and any studies reporting related health state utility data.

Figure 7: Economic evidence study selection flow chart



Appendix H Economic evidence tables

Economic evidence tables for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Table 22: Economic evidence tables

Study ID Country Type of study	Interventions and comparators	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
Dalziel 2010 Australia (& New Zealand) Cost-effectiveness and cost-utility analysis	Promotion of folic acid supplementation 1 month prior to and 3 months following conception through: d. multifaceted general population campaign (via healthcare & community staff, posters, newsletters, training, seminars, newspapers, ads, schools) ["General"] e. targeted campaign to disadvantaged women (indigenous women and women from low socio-economic backgrounds) ["Targeted"] f. brief clinician advice to women aged 18-48 years at	Women in the general population, focusing on 1 month prior to and 3 months following conception Economic modelling Source of effectiveness and intervention cost data: published seminal studies Source of unit costs: national or	Costs included: intervention (including programme administrators, health professionals, materials and so on), folic acid supplementation, training, equipment and supplies, lifetime costs of treating NTDs Total incremental costs: General: $20,513,724 Targeted: $2,005,818 Clinical advice: $4,076,215 Outcomes: Number of NTDs prevented Number of DALYs averted	ICERs: Cost/NTD prevented: General: $55,000 Targeted: $60,500 Clinical advice: $23,100 Cost/DALY averted (range in SA): General: $9,100 ($3,300-$18,900) Targeted: $12,300 ($4,800-$21,900)	• Perspective: healthcare & wider public sector (where relevant for delivery of interventions) • Currency: AUS$ (+NZ$) • Cost year: likely 2006 • Time horizon: 10 years for costs, lifetime for outcomes • Discounting: 5% • Applicability: Partial • Quality: Potentially serious methodological limitations

Study ID Country Type of study	Interventions and comparators	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
	a visit to an obstetrician /gynaecologist ["Clinical advice"] Current status (30% folic supplement uptake)	other published sources	Total NTDs prevented; DALYs averted: General: 21.0; 2,243 Targeted: 3.9; 163 Clinical advice: 10.1; 1,080	Clinical advice: $3,800 ($500-10,000)	
De Weerd 2004 The Netherlands Cost-effectiveness analysis	Preconception counselling by a GP about folic acid supplementation (assuming 50% and 75% uptake) No intervention (assuming zero uptake)	Women planning a pregnancy Economic modelling Source of effectiveness data: literature review Source of cost data: published	Costs included: healthcare professional time, mass media (posters and leaflets), folic acid supplementation, care for NTDs in 1st life year Total net cost per woman: 50% uptake: $22 75% uptake: $31 Outcome: number of NTDs averted	ICER: 50% uptake: $200,000/NTD averted 75% uptake: $184,848/NTD averted	• Perspective: healthcare • Currency: US$ • Cost year: 2002 • Time horizon: 1 year • Discounting: N/A • Applicability: Partial • Quality: Potentially serious methodological limitations

Study ID Country Type of study	Interventions and comparators	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
		studies, hospital records	Outcome per woman: 50% uptake: 0.0001 75% uptake: 0.0002		
Filby 2015 UK Cost-utility analysis	Universal offering to women planning a pregnancy & pregnant women <10 weeks Current scheme: No offering of Healthy Start Vitamin programme to women planning a pregnancy & pregnant women <10 weeks	Women planning a pregnancy; pregnant women <10 weeks Economic modelling Source of effectiveness & clinical input data: published UK study, national	Costs included: intervention (distribution & set up, vitamin acquisition), management of NTDs. Total incremental costs for eligible population in England: Women planning a pregnancy + <10 weeks pregnant: -£989,352 Pregnant women <10 weeks: £1,683,725	ICER: Offering to subgroups: Women planning pregnancy + <10 weeks pregnant: dominant Pregnant women <10 weeks: £7,126/QALY	• Perspective: NHS, public sector (NHS, local authority, central government); societal (public sector & individuals) • Currency: GBP (£) • Cost year: 2014 • Time horizon: lifetime for NTDs • Discounting: 3.5% • Applicability: Direct

Study ID Country Type of study	Interventions and comparators	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
		surveys, primary online survey Source of intervention and other cost data: national and local data, published evidence Source of unit costs: national & local sources	Outcomes: QALY estimated using EQ-5D (UK tariff) & other unclear ratings Incremental outcomes for eligible population in England: Women planning pregnancy + <10 weeks pregnant: 737 QALYs Pregnant women <10 weeks: 230 QALYs		• Quality: potentially serious methodological limitations
Grosse 2008 US Cost-utility analysis	Counselling and free folic acid supplements directly to women with a prior NTD-affected pregnancy identified through a birth defect–surveillance system Standard Care (birth defect-surveillance system)	Women with a pregnancy affected by NTD Non-comparative cohort study (N=459) & economic modelling Source of cost data: administrative records, staff time diaries and interviews	Costs included: staff time, folic acid supplements, amniocentesis, termination, delivery, care for people with NTDs, including education, developmental services, family's productivity losses Total/incremental costs: NR Outcome: QALY from prevented NTD-affected pregnancies (including live births, stillbirths and	ICER: $14,700/QALY gained from avoidance of NTD-affected pregnancies Best-worst case scenarios: $4,076 to $53,532/QALY Results sensitive to NTD	• Perspective: societal (healthcare, other agencies, patient, lost earnings from unpaid caregiving responsibilities • Currency: US$ • Cost year: 2003 • Time horizon: lifetime • Discounting: 3% • Applicability: Partial • Quality: Potentially serious methodological limitations

Study ID Country Type of study	Interventions and comparators	Study population Study design Data sources	Costs and outcomes: description and values	Results: Cost-effectiveness	Comments
		Source of unit costs: national & state	termination), estimated using HUI-2 and Canadian population preferences Total/incremental benefits: NR	recurrence risk & folic acid uptake	
Postma 2002 The Netherlands Cost-effectiveness analysis	Periconceptional supplementation of folic acid, recommended by gynaecologists (0.5 mg/day) Current status (35% folic acid uptake)	Women trying to become pregnant Economic modelling Source of effectiveness data: literature review Source of cost data: published study, national costs	Costs included: folic acid supplementation, lifetime costs of children with NTDs (healthcare & special education) Total/incremental costs: NR Outcome: Number of life years gained (from preventing NTDs and anencephaly) Total/incremental benefits: NR	ICER: €1,800/life-year gained Deterministic analysis: ICER ranged from intervention being dominant to €6,500/life-year gained	• Perspective: healthcare & special education • Currency: NLG (Dutch guilder) converted to Euros (€) • Cost year: 2000 • Time horizon: lifetime • Discounting: 4% • Applicability: Partial • Quality: Potentially serious methodological limitations

DALY: disability-adjusted life year; HUI: health utility index; ICER: incremental cost-effectiveness ratio; N/A: non-applicable; NR: not reported; NTD: neural tube defect; QALY: quality-adjusted life year

Appendix I Economic model

Economic model for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

This area was prioritised for de novo economic modelling. The committee selected to assess the cost-effectiveness of health technologies (such as apps), because these are the only interventions they considered for a recommendation which have promising evidence but are not currently in routine use in England. However, there was no adequate effectiveness evidence on health technologies to allow a meaningful and informative economic analysis to be carried out. Therefore, no economic model was developed for this review question.

.

Appendix J Excluded studies

Excluded studies for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Excluded effectiveness studies

One literature search was performed for the review questions in evidence reviews C and E. The excluded studies table below only lists the studies that were considered and then excluded at the full-text stage for this review (N=52). This does not include (N=11) that were considered and then excluded at the full-text stage for evidence review E.

Table 23: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Barchitta, Martina, Maugeri, Andrea, Magnano San Lio, Roberta et al. (2020) Dietary Folate Intake and Folic Acid Supplements among Pregnant Women from Southern Italy: Evidence from the "Mamma & Bambino" Cohort. International journal of environmental research and public health 17(2)	- Inappropriate study design *Not an intervention study. Study assessed prevalence of dietary folate intake and its determinants, folic acid supplement use and the effects on neonatal outcomes.*
Batra, Priya, Mangione, Carol M, Cheng, Eric et al. (2018) A Cluster Randomized Controlled Trial of the MyFamilyPlan Online Preconception Health Education Tool. American journal of health promotion : AJHP 32(4): 897-905	- Insufficient data on outcome of interest *Folic acid supplementation was a secondary outcome but no data was presented for this outcome. Study only mentioned that there were no statistical changes*
Bixenstine, Paul, Cheng, Tina, Cheng, Diana et al. (2015) Association Between Preconception Counseling and Folic Acid Supplementation Before Pregnancy and Reasons for Non-Use. Maternal & Child Health Journal 19(9): 1974-1984	- Inappropriate study design *Population based survey*
Bower C; Knowles S; Nicol D (1997) Changes in folate supplementation, and in serum and red cell folate levels in antenatal patients over the course of a health promotion project for the prevention of neural tube defects. Aust N Z J Obstet Gynaecol 3(37): 267-71	- No intervention of interest *The intervention had different components, including delivering to midwives and doctors pamphlets, posters and presentations. Women also received pamphlets, however not all of them saw it (the study reports that roughly 30% of women had seen it). Therefore, if only a minority of women received the intervention, the results cannot be used*

Study	Reason for exclusion
Cawley, Caroline, Buckenmeyer, Hannelore, Jellison, Trina et al. (2020) Effect of a Health System-Sponsored Mobile App on Perinatal Health Behaviors: Retrospective Cohort Study. JMIR mHealth and uHealth 8(7): e17183	- Does not address condition or domain being studied *Study assesses intake of prenatal vitamin but does not indicate if folic acid is included*
Chivu, C.M., Tulchinsky, T.H., Soares-Weiser, K. et al. (2008) A systematic review of interventions to increase awareness, knowledge, and folic acid consumption before and during pregnancy. American Journal of Health Promotion 22(4): 237-245	- Does not address condition or domain being studied *Systematic review with included studies that do not meet inclusion criteria due to wrong population, public health interventions or non-intervention studies*
Daly, Michael P, White, James, Sanders, Julia et al. (2022) Women's knowledge, attitudes and views of preconception health and intervention delivery methods: A cross-sectional survey. medRxiv: 2022052622275637	- Inappropriate study design *Not an intervention study. Study assessed women's knowledge of preconception health risk factors and population was all females registered with the GP practice.*
de Walle, H. E. K.; Cornel, M. C.; de Jong-van den Berg, L. T. W. (2002) Three Years after the Dutch Folic Acid Campaign: Growing Socioeconomic Differences. Preventive Medicine 35(1): 65-69	- No intervention of interest *Study assessed the impact of a mass media campaign for periconceptional folic acid intake*
Egen, V. and Hasford, J. (2003) Prevention of neural tube defects: Effect of an intervention aimed at implementing the official recommendations. Sozial- und Praventivmedizin 48(1): 24-32	- No population of interest *Health professionals were the target of the intervention, although uptake of folic acid was measured in mothers.*
Elsharkawy, N.B., Abdelaziz, E.M., Ouda, M.M. et al. (2022) Effectiveness of Health Information Package Program on Knowledge and Compliance among Pregnant Women with Anemia: A Randomized Controlled Trial. International Journal of Environmental Research and Public Health 19(5): 2724	- Does not address condition or domain being studied *The study does not focus on folic acid supplementation. The intervention focused on increasing uptake of iron supplementation in women with anaemia. Although, the iron supplement used includes folic acid, the focus of the study was not the folic acid.*
Evans, Sophie E, Mygind, Vanessa L, Peddie, Meredith C et al. (2014) Effect of increasing voluntary folic acid food fortification on dietary folate intakes and adequacy of reproductive-age women in New Zealand. Public Health Nutrition 17(7): 1447-1453	- No population of interest *Non-pregnant women who were not planning a pregnancy*

Study	Reason for exclusion
Flores, Alina L, Prue, Christine E, Daniel, Katherine Lyon et al. (2007) Broadcasting behavior change: A comparison of the effectiveness of paid and unpaid media to increase folic acid awareness, knowledge, and consumption among Hispanic women of childbearing age. Health Promotion Practice 8(2): 145-153	- No intervention of interest *Intervention was delivered at population-level using media such as television and radio stations*
Funnell, Gillian, Naicker, Kevin, Chang, John et al. (2018) A cross-sectional survey investigating women's information sources, behaviour, expectations, knowledge and level of satisfaction on advice received about diet and supplements before and during pregnancy. BMC pregnancy and childbirth 18(1): 182	- Inappropriate study design *Not an intervention study. Study assessed women's expectations, knowledge and sources of information, level of satisfaction with information received, and vitamin supplementation*
Golley, R, Pearce, J, Nelson, M et al. (2011) Children's lunchtime food choices following the introduction of food-based standards for school meals: observations from six primary schools in Sheffield. Public Health Nutrition 14(2): 271-278	- Does not address condition or domain being studied *Study assessed nutritional intake of children*
Gomes, F., King, S.E., Dallmann, D. et al. (2021) Interventions to increase adherence to micronutrient supplementation during pregnancy: a systematic review. Ann. New York Acad. Sci. 1493(1): 41-58	- Country not of interest *A systematic review with all included studies from low- and middle- income countries*
Honein, MA, Paulozzi, LJ, Mathews, TJ et al. (2001) Impact of folic acid fortification of the US food supply on the occurrence of neural tube defects. JAMA: Journal of the American Medical Association 285(23): 2981-3036	- No intervention of interest *Public health intervention. Fortification of the food chain with folic acid*
Howell, S R; Barnett, A G; Underwood, M R (2001) The use of pre-conceptional folic acid as an indicator of uptake of a health message amongst white and Bangladeshi women in Tower Hamlets, east London. Family practice 18(3): 300-3	- Inappropriate study design *Not an intervention study. Study compared folic acid use among white women versus Bangladeshi women*
Lassi, Z.S. and Bhutta, Z.A. (2015) Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. Cochrane Database of Systematic Reviews 2015(3): cd007754	- Country not of interest *Systematic review with all included studies conducted in low- and middle- income countries*

Study	Reason for exclusion
Liu, Shiliang, West, Roy, Randell, Edward et al. (2004) A comprehensive evaluation of food fortification with folic acid for the primary prevention of neural tube defects. BMC Pregnancy and Childbirth 4(1): 20	- No intervention of interest *Public health strategy for food fortification*
Maas, Veronique Y F, Koster, Maria P H, Ista, Erwin et al. (2020) Study design of a stepped wedge cluster randomized controlled trial to evaluate the effect of a locally tailored approach for preconception care - the APROPOS-II study. BMC public health 20(1): 235	- Insufficient data on outcome of interest *Study protocol*
Marsack, C R, Alsop, C L, Kurinczuk, J J et al. (1995) Pre-pregnancy counselling for the primary prevention of birth defects: rubella vaccination and folate intake. The Medical journal of Australia 162(8): 403-6	- Inappropriate study design *Not an intervention study. Study assessed pregnant women's knowledge of vaccination and folate intake and their source of information*
McDougall, Beth, Kavanagh, Kimberley, Stephenson, Judith et al. (2021) Health behaviours in 131,182 UK women planning pregnancy. BMC pregnancy and childbirth 21(1): 530	- Inappropriate study design *Not an intervention study. Study assessed the health behaviours of women planning a pregnancy*
Meijer W, de Smit D, Jurgens R et al. (2005) Improved periconceptional use of folic acid after patient education in pharmacies: Promising results of a pilot study in the Netherlands. International Journal of Pharmacy Practice (IJPP) 13: 47-51	- Inappropriate study design *Study design does not meet protocol inclusion criteria (Cross-sectional study design)*
Molton, JS, Pang, Y, Wang, Z et al. (2016) Prospective single-arm interventional pilot study to assess a smartphone-based system for measuring and supporting adherence to medication. BMJ open 6(12nopagination)	- Does not address condition or domain being studied *Study addresses medication adherence for tuberculosis*
Oza-Frank, Reena, Kachoria, Rashmi, Keim, Sarah A et al. (2015) Provision of specific preconception care messages and associated maternal health behaviors before and during pregnancy. American Journal of Obstetrics & Gynecology 212(3): 372e1-8	- Inappropriate study design *Study design does not meet protocol inclusion criteria (Cross-sectional study design)*
Pastuszak A, Bhatia D, Okotore B et al. (1999) The effectiveness of pre-conceptional	- Unable to retrieve full text

Study	Reason for exclusion
counselling on women's compliance with folic acid. In: Maternal-fetal toxicity.	*Study was identified from the reference list of another study, but the full text could not be retrieved. From the citation, it is assumed to be a book chapter*
Pastuszak, A, Bhatia, D, Okotore, B et al. (1999) Preconception counseling and women's compliance with folic acid supplementation. Canadian family physician Medecin de famille canadien 45: 2053-7	- Insufficient data on outcome of interest *Study does not present adequate comparison data between the intervention and control groups. Data was presented for users of folic acid preconception in the control group, whereas in the intervention group, data was presented for users of folic acid at the time of follow-up call and for users of folic acid in a subgroup of women who had conceived.*
Phelan, S; Abrams, B; Wing, RR (2019) Prenatal Intervention with Partial Meal Replacement Improves Micronutrient Intake of Pregnant Women with Obesity. Nutrients 11(5)	- Does not address condition or domain being studied *Not focused on supplementation. Study focuses on micronutrient intake which includes food, beverages and supplements. Vitamin intake from supplements were not presented separately*
Pring, M. Sillender, D. W. (2000) How effective was the Health Education Authority's folic acid campaign?. Journal of Obstetrics and Gynaecology 20(3): 271-276	- No intervention of interest *Television and magazine campaign*
Quinn, GP, Thomas, KB, Hauser, K et al. (2009) Evaluation of educational materials from a social marketing campaign to promote folic acid use among Hispanic women: insight from Cuban and Puerto Rican ethnic subgroups. Journal of Immigrant & Minority Health 11(5): 406-414	- Insufficient data on outcomes of interest *Data was presented for vitamins which contains folic acid, but the amount of folic acid contained in the multivitamin supplement was not specified*
Robbins, James M, Cleves, Mario A, Collins, H Breck et al. (2005) Randomized trial of a physician-based intervention to increase the use of folic acid supplements among women. American journal of obstetrics and gynecology 192(4): 1126-32	- No population of interest *Excludes women who were currently pregnant or visiting clinic for preconception or nonroutine care*
Scott, P.A., Quotah, O.F., Dalrymple, K.V. et al. (2021) Community pharmacist-led interventions to improve preconception and pregnancy health: A systematic review. Pharmacy 9(4): 171	- Does not address condition or domain being studied *Systematic review study with all included studies conducted in LMICs or focused on smoking*

Study	Reason for exclusion
	cessation except Meijer 2015 is a cross-sectional study
Shumi, Yamamoto, Yoshinao, Wada, Yamamoto, Shumi et al. (2018) Awareness, use and information sources of folic acid supplementation to prevent neural tube defects in pregnant Japanese women. Public Health Nutrition 21(4): 732-739	- Inappropriate study design *Not an intervention study. Study assessed women's knowledge, source of information and use of folic acid*
Stephenson, Judith, Patel, Dilisha, Barrett, Geraldine et al. (2014) How do women prepare for pregnancy? Preconception experiences of women attending antenatal services and views of health professionals. PloS one 9(7): e103085	- Inappropriate study design *Not an intervention study. Study assessed knowledge and uptake of preconception care including folic acid use*
Temel, S., Van Voorst, S.F., Jack, B.W. et al. (2014) Evidence-based preconceptional lifestyle interventions. Epidemiologic Reviews 36(1): 19-30	- Does not address condition or domain being studied *Systematic review study with 3 of the included studies (de Weerd 2002, Robbins 2005 and Watkins 2004) relevant to this review and have been included as individual studies. Other studies included in the systematic review did not meet inclusion criteria due to wrong population, having a public health intervention or no outcomes of interest (for example, pregnancy outcomes)*
van der Windt, M., van der Kleij, R.M., Snoek, K.M. 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	- Insufficient data on outcome of interest *No figures presented on folic acid use and chart presented was lumped as total for all participants including men*
Watson, M.J., Watson, L.F., Bell, R.J. et al. (1999) A randomized community intervention trial to increase awareness and knowledge of the role of periconceptional folate in women of child-bearing age. Health Expectations 2(4): 255-265	- No intervention of interest *Public health intervention: informational campaign using leaflets, posters and brochures targeted at all women, not just those contemplating pregnancy.*

LMICs: low and middle income countries.

Excluded economic studies

Study	Reason for exclusion
Bhutta, Z.A., Das, J.K., Rizvi, A. et al. (2013) Evidence-based interventions for improvement of maternal and child nutrition: What can be done and at what cost?. The Lancet 382(9890): 452-477	Costs refer to no OECD countries
Shlobin, N.A., LoPresti, M.A., Du, R.Y. et al. (2021) Folate fortification and supplementation in prevention of folate-sensitive neural tube defects: A systematic review of policy. Journal of Neurosurgery: Pediatrics 27(3): 294-310	Systematic review (individual studies checked)
Szewczyk, Z., Holliday, E., Dean, B. et al. (2021) A systematic review of economic evaluations of antenatal nutrition and alcohol interventions and their associated implementation interventions. Nutrition Reviews 79(3): 261-273	Systematic review (individual studies checked)
Yi, Y., Lindemann, M., Colligs, A. 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): 1391-1400	Systematic review (individual studies checked)

Appendix K Research recommendations – full details

Research recommendations for review question: What interventions are effective to increase uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Research recommendation

What is the clinical and cost effectiveness of digital technologies (for example, apps, social media, online support groups) to increase the uptake of folic acid supplementation before and during the first 12 weeks of pregnancy?

Why this is important

Folic acid supplementation before and during pregnancy can prevent neural tube defects (NTDs) but uptake of folic acid supplementations is relatively low. Cost-effective and accessible strategies such as using digital technologies to increase the daily uptake of a 400 microgram folic acid supplement by all people who could become pregnant and for the first 12 weeks of pregnancy are required.

Rationale for research recommendation

Table 24: Research recommendation rationale

Importance to 'patients' or the population	To reduce the risk of neural tube defects (NTDs), current guidance recommends that all people who could become pregnant should take a daily 400 microgram folic acid supplement before conception and until the 12th week of pregnancy. However, compliance with this guidance is sub-optimal (around 30%) and the preventative benefits of taking a folic acid supplement are not being met for the majority of pregnancies.
Relevance to NICE guidance	Current NICE guidance is that all people who could become pregnant should take a daily 400 microgram folic acid supplement before conception and until the 12th week of pregnancy in order to reduce the risk of neural tube defects (NTDs).
Relevance to the NHS	Cost-effective and accessible strategies to increase the daily uptake of a 400-microgram folic acid supplement by all people who could become pregnant and for the first 12 weeks of pregnancy are required.
National priorities	High
Current evidence base	No evidence for digital technologies was identified in the review.
Equality considerations	Ethnicity and socio-economic factors

NICE: National Institute for Health and Care Excellence.

Modified PICO table

Table 25: Research recommendation modified PICO table

Population	Inclusion: • Women planning to become pregnant • Pregnant women during the first 12 weeks of a single or multiple pregnancy

Intervention	Digital technologies (for example, apps, social media, online support groups) to increase uptake of folic acid supplementation
Comparator	• Placebo/control • Any other intervention to increase uptake of folic acid supplementation
Outcome	Primary outcomes • Changes in folic acid supplementation uptake rate Secondary outcomes • Changes in attitude, confidence and knowledge as part of people's intention to change behaviour • Unintended consequences of the interventions: • Increase in inequalities • Supplementation wastage • 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	RCT
Timeframe	Short- and medium-term follow-up
Additional information	Sub-group analysis: 1. Age • Under 40 years of age • Over 40 years of age 2. Socio economic status and deprivation (using IMD) 3. Comorbidities 4. Geographical variation, for example places without adequate provision of primary care (outside cities). 5. Ethnicity • White/White British • Asian/Asian British • Black/African/Caribbean/Black British • Mixed/Multiple ethnic groups • Other ethnic group

QALY: quality adjusted life years; EQ-5D: European Quality of Life Five Dimension; PICO: population, Intervention, Comparison and Outcome; SF-6D: six-dimensional health state short form