

Periconceptional supplementation with folate and/or multivitamins for preventing neural tube defects (Review)

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TABLE OF CONTENTS

ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
BACKGROUND	2
OBJECTIVES	3
CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW	3
SEARCH METHODS FOR IDENTIFICATION OF STUDIES	3
METHODS OF THE REVIEW	4
DESCRIPTION OF STUDIES	4
METHODOLOGICAL QUALITY	4
RESULTS	4
DISCUSSION	5
AUTHORS' CONCLUSIONS	6
FEEDBACK	7
POTENTIAL CONFLICT OF INTEREST	7
ACKNOWLEDGEMENTS	7
SOURCES OF SUPPORT	7
REFERENCES	8
TABLES	10
Characteristics of included studies	10
Characteristics of excluded studies	13
ADDITIONAL TABLES	13
Table 01. Dissemination trial: % women aware of folate/NTD association	13
ANALYSES	13
Comparison 01. All trials	13
Comparison 02. Occurrent neural tube defects	13
Comparison 03. Folate prevention of recurrent neural tube defects	14
Comparison 04. Multivitamin prevention of recurrent neural tube defects	14
Comparison 05. Folate vs multivitamin prevention of recurrent neural tube defects	14
Comparison 06. Multivitamin vs Folate/multivitamin prevention of recurrent neural tube defect	14
Comparison 07. Folate vs Folate/Multivitamin prevention of recurrent neural tube defect	14
INDEX TERMS	14
COVER SHEET	14
GRAPHS AND OTHER TABLES	16
Analysis 01.01. Comparison 01 All trials, Outcome 01 Neural tube defect	16
Analysis 01.02. Comparison 01 All trials, Outcome 02 Miscarriage	16
Analysis 01.03. Comparison 01 All trials, Outcome 03 Ectopic pregnancy	17
Analysis 01.04. Comparison 01 All trials, Outcome 04 Stillbirth (Fetal death)	17
Analysis 01.05. Comparison 01 All trials, Outcome 05 Multiple gestation	18
Analysis 01.06. Comparison 01 All trials, Outcome 06 Limb reduction defects	18
Analysis 01.07. Comparison 01 All trials, Outcome 07 Conotruncal heart defects	19
Analysis 01.08. Comparison 01 All trials, Outcome 08 Orofacial clefts	19
Analysis 01.09. Comparison 01 All trials, Outcome 09 Other birth defects	20
Analysis 01.10. Comparison 01 All trials, Outcome 10 Conception	20
Analysis 01.11. Comparison 01 All trials, Outcome 11 Nausea, vomiting and vertigo	21
Analysis 02.01. Comparison 02 Occurrent neural tube defects, Outcome 01 Neural tube defect	21
Analysis 03.01. Comparison 03 Folate prevention of recurrent neural tube defects, Outcome 01 Neural tube defect	22
Analysis 04.01. Comparison 04 Multivitamin prevention of recurrent neural tube defects, Outcome 01 Neural tube defect	22
Analysis 05.01. Comparison 05 Folate vs multivitamin prevention of recurrent neural tube defects, Outcome 01 Neural tube defect	23

Analysis 06.01. Comparison 06 Multivitamin vs Folate/multivitamin prevention of recurrent neural tube defect,	23
Outcome 01 Neural tube defect	
Analysis 07.01. Comparison 07 Folate vs Folate/Multivitamin prevention of recurrent neural tube defect, Outcome 01	24
Neural tube defect	

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ABSTRACT

Background

Neural tube defects arise during the development of the brain and spinal cord.

Objectives

The objective of this review was to assess the effects of increased consumption of folate or multivitamins on the prevalence of neural tube defects periconceptionally (that is before pregnancy and in the first two months of pregnancy).

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group trials register. Date of last search: April 2001.

Selection criteria

Randomised and quasi-randomised trials comparing periconceptional supplementation by multivitamins with placebo, folate with placebo, or multivitamins with folate; different dosages of multivitamins or folate; prepregnancy dietary advice and counselling in primary care settings to increase the consumption of folate-rich foods, or folate-fortified foods, with standard care; increased intensity of information provision with standard public health dissemination.

Data collection and analysis

Two reviewers assessed trial quality and extracted data.

Main results

Four trials of supplementation involving 6425 women were included. The trials all addressed the question of supplementation and they were of variable quality. Periconceptional folate supplementation reduced the incidence of neural tube defects (relative risk 0.28, 95% confidence interval 0.13 to 0.58). Folate supplementation did not significantly increase miscarriage, ectopic pregnancy or stillbirth, although there was a possible increase in multiple gestation. Multivitamins alone were not associated with prevention of neural tube defects and did not produce additional preventive effects when given with folate.

One dissemination trial, a community randomised trial, was identified involving six communities, matched in pairs, and where 1206 women of child-bearing age were interviewed following the dissemination intervention. This showed that the provision of printed material increased the awareness of the folate/neural tube defects association by 4%, (odds ratio 1.37, 95% confidence interval 1.33 to 1.42).

Authors' conclusions

Periconceptional folate supplementation has a strong protective effect against neural tube defects. Information about folate should be made more widely available throughout the health and education systems. Women whose fetuses or babies have neural tube defects should be advised of the risk of recurrence in a subsequent pregnancy and offered continuing folate supplementation. The benefits and risks of fortifying basic food stuffs, such as flour, with added folate remain unresolved.

PLAIN LANGUAGE SUMMARY

Supplements of multivitamins or folate before pregnancy and during the first two months help protect against neural tube defects

The neural tube is the structure from which a baby's brain and spinal cord develop. Neural tube defects (NTDs) are a group of abnormalities that occur in the spine or brain of the baby during pregnancy, causing severe mental and physical disability. The review of trials found that folate, taken as a supplement before pregnancy and in the first two months, is effective in protecting against neural tube defects. Folate did not increase risk of miscarriage, ectopic pregnancy (pregnancy outside the uterus) or stillbirth. Folate may increase the chance of multiple pregnancies. Multivitamins alone do not give protection against NTDs.

BACKGROUND

The neural tube defects (NTDs) - anencephaly [the total or partial absence of the cranial vault, the covering skin and the brain tissue], spina bifida [non-closure of the spine resulting in herniation or exposure of the spinal cord, the meninges or both; in some cases together with hydrocephalus], encephalocele [herniation of meninges and brain tissue outside the cranium, covered by normal or atrophic skin] - are congenital malformations which arise during the development of the brain and spinal cord. A band of cells along the dorsal surface of the embryo develops into a groove then a hollow tube. This process is completed within a month of fertilization (by the sixth week after the last menstrual period). Incomplete closure of the neural tube causes NTDs. Anencephaly is incompatible with survival: the other two NTDs have a high perinatal and infant mortality. Impairments in surviving children (incontinence, reduced mobility and sensation, learning difficulties) vary from extreme to mild - but are commonly severe - depending on the location of the defect, its size, the extent of neural tissue damage and the degree of accompanying hydrocephalus [abnormal increase in the amount of fluid within the ventricles of the brain].

NTDs may occur as isolated defects or with other birth defects. A number of multiple malformation syndromes (eg Joubert, Schisis association, HARD syndrome) commonly include one of these defects. Although some neural tube defects occur in association with autosomal trisomies, and rare recessive, dominant and X-linked forms are described, for the majority there is no known Mendelian or chromosomal etiology. Thus, there is evidence of substantial heterogeneity in their aetiology [causes] (Winter 1989).

Second trimester screening for NTDs by maternal serum alpha-fetoprotein estimation or fetal ultrasound examination can identify over 80% of affected pregnancies and identification is usually followed by termination of pregnancy. While this has led to a fall in the birth prevalence of NTDs (Chan 1993) it has not prevented the development of these defects in early pregnancy nor the parental grief associated with having an affected pregnancy.

Extensive descriptive epidemiology of NTDs summarised by Elwood, Little and Elwood (Elwood 1992) has led to the conclusion that both environmental and genetic factors are likely to be impor-

tant. For example: there are striking geographical variations, both between and within countries, in the prevalence at birth of NTDs: for instance in China, the prevalence at birth is 60/10,000 in a northern province and 10/10,000 in a southern province (Berry 1999). In Australia, prevalence data including terminations is estimated to be 16/10,000 (Lumley 2001 in press). In places where the prevalence is high there are marked social class differences, with an inverse social class gradient; the occurrence of an NTD is associated with a greatly increased risk of recurrence in subsequent pregnancies.

A study of multivitamin supplementation beginning before pregnancy and continuing through the first three months (periconceptional), in women with a prior pregnancy affected by an NTD, found significantly fewer NTDs in supplemented offspring: odds ratio (OR) 0.11 (95% confidence interval (CI) 0.01-0.85) (Smithells 1980b; Smithells 1981; Smithells 1983). In the absence of randomisation, which had not been permitted by an institutional ethics committee (Smithells 1980a), the social and reproductive differences between those who took the multivitamin preparation and the control group, who were either pregnant already or refused to take the multivitamin, led to uncertainty as to the effectiveness of the intervention (Wald 1984). In addition, it remained unclear which micronutrient or combination of micronutrients might be effective.

At the same time another non-randomised intervention study (Laurence 1980), found that recurrence of neural tube defects was less frequent in women with poor diets receiving pre-pregnancy dietary counselling (3/103) than among women who received no such counselling (5/71).

With one exception (Mills 1989), case control, cohort and non-randomised intervention studies undertaken and reported since 1980 have identified decreased risks of NTD in offspring of women with higher dietary intakes of folate, and of women who have taken multivitamin or folic acid supplements periconceptionally (Mulinare 1988; Bower 1989; Werler 1993; Shaw 1995; Friel 1995; Milunsky 1989; Vergel 1990; Berry 1999). Risk estimates ranged from 0 to 0.7 and the 95% confidence intervals around the risk estimates for many of these studies excluded unity (see Bower 1989).

In the last three years, new evidence has been produced for disturbed homocysteine metabolism as a factor in neural tube defects, based particularly on studies of the thermolabile methylenetetrahydrofolate reductase mutation (Fowler 1997) which is also of importance in adult vascular disease (Rimm 1998). Current research on the role of folate, B6 and B12 in homocysteinaemia (Verhoef 1996) shows promise of being able to link these genetic and environmental factors, though the heterogeneity of NTDs may preclude a total explanation by any single mechanism.

OBJECTIVES

The primary objective is to identify whether the prevalence of neural tube defects can be reduced by increased consumption of multivitamins or folate before pregnancy and in the first two months of pregnancy (periconceptionally).

Other objectives:

1. to identify whether the prevalence at birth of other birth defects can be reduced by the same intervention;
2. to identify whether the same intervention changes fertility or fetal survival;
3. to compare strategies for increasing periconceptional consumption of multivitamins or folate;
4. to compare strategies for increasing knowledge about the benefits of periconceptional consumption of multivitamins or folate.

This review will not address the provision of nutritional advice, counselling, or supplementation during pregnancy.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All studies with randomised or quasi-randomised allocation were considered.

Types of participants

- Women planning to become pregnant who had already had an affected pregnancy, ie known conception of a fetus with a neural tube defect, whether or not the pregnancy resulted in a birth.
- Women planning to become pregnant who had not had a previous affected pregnancy, or had not been pregnant before.
- Health practitioners in trials of strategies to change knowledge, attitudes and behaviour.
- Women of childbearing age and other population samples in trials of strategies to change knowledge, attitudes and behaviour.

Types of intervention

Trials were included if they compared periconceptional supplementation with multivitamins and placebo, folate with placebo, or multivitamins with folate; if they compared periconceptional

supplementation at different dosages of multivitamins or folate; if they compared prepregnancy dietary advice and counselling in primary care settings to increase the consumption of folate-rich foods, or folate-fortified foods, with standard care; if they compared increased intensity of information provision/marketing strategies to general practitioners, pharmacists or communities, with standard public health dissemination.

Types of outcome measures

- (i) neural tube defects, isolated and in association with other malformations;
- (ii) facial clefts, limb reduction defects, conotruncal heart defects [abnormalities in the way the main blood vessels coming out from the heart separate from one another], urogenital defects; all other birth defects;
- (iii) spontaneous abortion;
- (iv) multiple pregnancy;
- (v) preterm birth (< 37 weeks' gestation);
- (vi) perinatal and infant mortality (stillbirths, neonatal deaths, all perinatal deaths, postneonatal deaths, infant deaths);
- (vii) time to conception;
- (viii) blood/tissue levels of vitamins, folate;
- (ix) measures of knowledge, attitudes, behaviour of primary care practitioners with respect to the prevention of NTDs;
- (x) measures of knowledge, attitudes, behaviour of women of childbearing age with respect to the prevention of NTDs;
- (xi) measures of the knowledge and attitudes of the population with respect to the prevention of NTDs.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

This review has drawn on the search strategy developed for the Cochrane Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service.

Relevant trials, which are identified through the Group's search strategy, are entered into the Group's Specialised Register of Controlled Trials. Please see Review Group's details for more detailed information. Date of last search: April 2001.

In addition, a broad and non-specific search using the term 'neural tube defects' is carried out every six months.

METHODS OF THE REVIEW

Data extraction:

Data were extracted from the published reports by two reviewers independently (L Watson and M Watson), without blinding as to journal, author, or research group. For each trial the following aspects were documented: (i) country of origin, (ii) study population (including whether the trial was intended to prevent occurrent or recurrent NTDs), (iii) inclusion and exclusion criteria, (iv) the nature of the intervention(s), compliance, and withdrawals, (v) details of the study design (including method of allocation, individual or cluster randomisation, blinding, method of outcome assessment), (vi) outcome measures.

Additional information was sought from the individual investigators where the published information did not contain the required detail.

Quality assessment:

The methodological quality of the studies included was assessed using the scheme described in the Cochrane Handbook which assesses the quality of random allocation.

Data analysis:

- The statistical methods used were those described by Yusuf (Yusuf 1985).
- In all pooled analyses, tests for heterogeneity were performed (Cochran 1954) and relative risks using random effects analysis are presented.
- A secondary analysis analysed outcomes for women with a prior NTD (recurrent cases), and those with no prior NTD (occurrent cases) separately.

DESCRIPTION OF STUDIES

See tables 'Characteristics of included studies' and 'Characteristics of excluded studies'.

METHODOLOGICAL QUALITY

The methodological quality of the four included supplementation studies was variable. In two of the four prevention trials, the method of randomisation was unclear. Two had no clear sample size justification. Another did not reach its planned sample size because of large and unanticipated changes in the prevalence of the primary outcome.

As the primary outcome was a major structural malformation of the fetus/infant, concealment of the allocation was less important than it might be in other trials.

Serial publication of data from one of the trials made it difficult to be certain of the denominators for all outcomes.

The dissemination trial was a community randomised trial involving six communities, matched in pairs and was of high quality. The analysis incorporated the effects of the pairs, the community sampling unit and the age/location population sampling fraction. The data are not included in the tables and figures since adjustment for cluster effect was not possible in the current analytic methods.

RESULTS

Periconceptional folate supplementation reduces the prevalence of neural tube defects substantially: relative risk (RR) 0.28 (95% confidence interval (CI) 0.13, 0.58). The reduction is similar for occurrent defects (those where the mother has not had a previously affected fetus or infant) RR 0.07 (95% CI 0.00, 1.32) and for recurrent defects (where the mother has had a previously affected infant) RR 0.31 (95% CI 0.14, 0.66). The number needed to treat (NNT) for folate prevention of an NTD is 847.

The trials had very low power to identify differences in limb reduction defects RR 0.59 (95% CI 0.04, 8.34), conotruncal defects RR 0.74 (95% CI 0.16, 3.32), or orofacial clefts RR 0.76 (95% CI 0.24, 2.37) or all other major birth defects combined RR 0.76 (95% CI 0.38, 1.51).

Folate supplementation was not associated with an increase in conception RR 1.02 (95% CI 0.97, 1.07). No adverse effects of the folate supplementation were detected in terms of any statistically significant increase in miscarriage RR 1.12 (95% CI 0.98, 1.29), or ectopic pregnancy RR 1.09 (95% CI 0.47, 2.55); nor was the reduction in stillbirth RR 0.78 (95% CI 0.34, 1.78) statistically significant. The relatively large increase in multiple gestation which was also not statistically significant - RR 1.40 (95% CI 0.93, 2.11) - was consistent in the three trials which reported data on this outcome.

Women in an early recruitment subgroup of one trial (Czeizel 1994) were less likely to experience vertigo, nausea or vomiting in the first trimester of pregnancy; RR 0.46 (95% CI 0.26, 0.91).

The dose of folate in the trials ranged from 0.36 mg/day to 4 mg/day. It is unlikely that any trials will be carried out to identify the minimal effective dose.

Evidence on the effectiveness of multivitamins in preventing recurrent neural tube defects is available from two trials only. There was no statistically significant reduction when multivitamins alone were compared with placebo RR 0.61 (95% CI 0.26, 1.45), when multivitamins were compared with multivitamins plus folate RR 2.05 (95% CI 0.67, 6.26), or when folate was compared with multivitamins plus folate RR 0.49 (95% CI 0.09, 2.66). When folate alone was compared with multivitamins alone there was a reduction with folate RR 0.27 (95% CI 0.07, 1.08) consistent with the overall finding but which did not quite reach statistical significance.

In the dissemination trial, 1197 women were interviewed prior to the intervention, and of these 12.4% (adjusted for the cluster and population sampling unit) were aware of folate and NTDs. After the intervention, there was not only a significant background increase of 3.4% ($p = 0.02$) in folate awareness since the pre-intervention survey ($n = 603$) but also a significant additional increase of 4.0% (odds ratio adjusted for cluster randomisation 1.37, 95% CI 1.33, 1.42) due to the intervention itself ($n = 603$). Only 70% of women who were aware that folate could prevent NTDs, also knew that folate was required periconceptionally for effective prevention.

DISCUSSION

The evidence about preventing recurrence of neural tube defects (NTDs) is so strong that recommendations for offering routine folate supplementation (4 mg/day) to women after an affected pregnancy are already widely supported as public health policy.

There was no evidence of a significant increase in conceptions with folate supplementation, and no significant differences in miscarriage, ectopic pregnancy or stillbirth. The increase in multiple pregnancies which did not reach statistical significance but which was consistent in three trials could be described as moderate evidence of a worrying effect - a 40% increase in multiple births could alter the relative risks and benefits of supplementation markedly.

The reviewers' concern about a possible increase in multiple births comes from the much commoner adverse outcomes of multiple pregnancies and the calculation that the numbers needed to treat for one additional twin confinement is 175 compared with 847 to prevent one NTD (Lumley 2001 in press).

With respect to primary prevention of occurrent NTDs, the evidence for prevention by folate supplementation is equally strong but there are problems with implementation. The first of these is the dose of folate since in the only primary prevention trial - in Hungary - the dose was 0.8 mg (Czeizel 1994), an amount not commonly available in other places. Since the recurrence prevention studies with non-randomised controls achieved comparable levels of prevention with a daily dose of 0.36 mg, most national policy statements have opted for 0.4 mg/day as the recommended intake for all women contemplating pregnancy. The large cohort study conducted in China, and originally planned as a trial (Erickson 1991), used this dose and showed consistent and significant reductions in the occurrence of NTDs (Berry 1999).

The second problem is the slow spread of information to women of child-bearing age, and to primary care providers, about the need for periconceptional folate, as shown in surveys of women of childbearing age and family practitioners. There are recent examples from the US (Centres for Disease Control and Prevention - CDCP 1997), Australia (Bower 1997a; Bower 1997b), Ireland (Sayers 1997), Scotland (McGovern 1997) and the UK (Krischer

1997). The one dissemination trial found that the provision of printed educational material can increase folate awareness among women of child bearing age (Watson 1999). This study found that women had increased concerns having seen folate promotional material and after being interviewed about it but concluded the results were consistent with an appropriate adaptive response to sensitive health information (Watson 1999). No economic evaluation was carried out.

A third factor is the high proportion of pregnancies which are unplanned so that action on folate supplementation - whether by diet or tablet - triggered by planning a pregnancy will be irrelevant to as many as half of all pregnancies in some areas (McGovern 1997).

One small trial (Daly 1997) measured the incremental change in red-cell folate in women with less than optimal red-cell folate supplemented with different folate dosages in a randomised trial. The median red-cell folate after a six month trial (with non-compliers excluded) was 311 mcg/L for those on placebo, 375 mcg/L for those receiving an additional 100 mcg/day, 475 mcg/L for those receiving an additional 200 mcg/day and 571 mcg/L for those receiving 400 mcg/day.

There is evidence from other studies of higher bioavailability of folic acid as a supplement or as a food additive than naturally occurring folate in foods (Inst of Med 1998). A small trial in Ireland (Cuskelly 1996) has thrown some doubt on the effectiveness of dietary advice and the provision of foods naturally rich in folate to achieve high red-cell folate levels. Women were asked to avoid folic acid supplements and folate fortified foods for three months prior to the commencement of the study and were then randomised to one of four different intervention groups or to a control group. The red cell folate at the end of a three month period, excluding those with poor compliance, was 335 (sd 60) mcg/L in the control group, 399 (sd 74) mcg/L in those receiving dietary advice only, 394 (sd 101) mcg/L in those provided with foods rich in folate, 498 (sd 135) mcg/L in those provided with food fortified with additional folate, and 492 (sd 118) mcg/L in those given a folate supplement (tablet) of 0.4 mg/day. A trial in the Netherlands (Brouwer 1999) showed a diet rich in vegetables and citrus fruit to be equally effective in increasing plasma and red blood cell folate as supplementation of folic acid. The red cell folate at the end of a four week period was 345 (sd 69) nmol/L in the placebo group (no additional folate or folic acid), 382 (sd 70) nmol/L in the folic acid group (0.5 mg folic acid supplement every second day) and 400 (sd 114) nmol/L in the dietary folate group (estimated 0.35 mg folate per day).

Thus there is still uncertainty whether the usual diet, or the usual diet plus dietary advice on increasing the intake of foods naturally rich in folate, consistently provides the 0.4 mg/day recommended for the majority of women in developed countries. Even less is known about the adequacy of diet of other population groups

such as ethnic minorities and indigenous peoples in developed or developing countries.

The randomized controlled trials are too small to contribute to the evidence base on overconsumption of folate or interactions of folate with prescription drugs. A recently published, large, case-control study has demonstrated an increased relative risk of birth defects associated with a variety of drugs, especially drugs used in epilepsy but also antimalarials, which alter folate metabolism (Hernandez-Diaz 2000).

The only known serious risk to women not taking such prescribed drugs is the possibility that folate may mask signs of vitamin B12 deficiency and allow some neurological symptoms to appear. This is most unlikely to happen in women of child-bearing age, but it can occur.

Two additional strategies for increasing folate intake by all women 'at risk' of becoming pregnant are the production and sale of foods fortified with extra folate, and the addition of folate to basic food components such as flour. The first of these strategies is acceptable in many countries, but given the choice of foods and the likely additional costs it is not a strategy to ensure prevention for the majority of women. Also, some countries still have, in principle, opposition to making health claims about foods. Discussion about the second strategy, modifying a basic food component such as flour by added folate, centres on assessment of the benefits and risks of additional folate for different age-groups and the problem of variations in consumption. The areas of concern are those which might apply to people who do not benefit directly from NTD prevention. Older people who are most at risk of vitamin B12 deficiency are one such group. Concern about variations in consumption apply particularly to children and adolescents who would receive additional folate over a long period of time. Possible benefits of increasing folate consumption for everyone have been argued in relation to reducing mid-life cardiovascular disease (Rimm 1998). Trials of folate and B12 for prevention of cardiovascular disease are in progress but have not yet (April 2001) been reported.

The US implemented both strategies from January 1998, requiring folic acid to be added to enriched cereal grain products such as flours, corn meals, pasta and rice, and permitting breakfast cereals to be fortified with up to 0.4 mg folic acid per serving (Centers for Disease Control and Prevention - CDCP 1997). Assessing the benefits and risks is made more complicated by genetic polymorphisms [differences in enzyme structure and activity] influencing folate metabolism (Whitehead 1997), suggesting that there is no single solution for all regions and countries.

This review which is about NTD prevention is not able to, or intended to, review the evidence about the risks and benefits of folate in all circumstances. However, the fact that national bodies have made different decisions about adding folate to basic food components shows the decision to be a complex one.

AUTHORS' CONCLUSIONS

Implications for practice

All women who have a fetus diagnosed as having a neural tube defect in pregnancy, or give birth to an infant with a neural tube defect, need to be given information about the risk of recurrence in a subsequent pregnancy, to be advised of the protective effect of preconceptional folate supplementation, and offered continuing supplementation (4mg/day).

All health contacts involving the provision of contraception to women offer the opportunity for a reminder of the protective effects of a folate-rich diet, information about how this can be achieved, and the reminder that it needs to start two months before conception.

Information on the protective effects of a folate-rich diet needs to be incorporated into nutrition and health education at secondary school level.

It is still unclear whether adequate folate to maximise the prevention of neural-tube defects can be provided by informed changes in the pattern of food consumption to a folate-rich diet.

Intersectoral activity on appropriate food labelling, advertising and marketing of foods with added folate is a priority, as is attention to ethnic and cultural differences in the selection of foods to which this should apply.

While the likely benefits of fortifying basic food components such as flour with additional folate are clearly established in terms of the prevention of neural tube defects, the benefits and risks of food fortification with folate to other people in the community remain unresolved.

Given past fluctuations over time in the prevalence at birth of neural tube defects, and the increased likelihood of their early prenatal diagnosis, monitoring the effectiveness of interventions to increase folate uptake by trends in births of affected infants has the potential to be seriously misleading. Birth defects monitoring systems need to have surveillance systems in place for effective capture of all the relevant events.

Implications for research

A priority for new trials is trials of the dissemination of information about the protective effects of folate supplementation so that effective, and cost-effective strategies can be implemented.

It seems most unlikely that any new primary prevention trials to assess the protective effect of folate in relation to neural tube defects or other birth defects will be carried out - even to clarify the unanswered questions about the minimal dose required - because of the strength of the existing evidence. Given the consistency of effects identified in case-control and cohort studies with those in the randomised trials, information from study designs other than

randomised trials (cohort and case-control studies) will be needed to assess the possibility of side-effects of folate supplementation such as an increase in multiple births, as well as the role of folate in the prevention of other birth defects, and further information about the protective dose.

Trials, some of which are already underway, to measure the effectiveness of folate supplementation in the prevention of mid-life cardiovascular disease are expected to clarify the potential benefits of an increased folate intake for men and women in adult life. These findings will contribute to more informed decisions about the risks and benefits of fortification of basic food components.

FEEDBACK

Selinger, October 2006

Summary

How do the review authors extrapolate the evidence from mothers with previously affected pregnancies to women planning their first pregnancy?

(Summary of comment from Mark Selinger, October 2006)

Author's reply

The reasons why we combined data from women planning their first child (Czeizel 1994) with data from women who had already had an infant with a neural tube defect were:

1. The one trial involving women having their first child (Czeizel 1994) was very large compared with the three trials in women with a past history of a baby with a neural tube defect, and it was close to showing a significant effect (a reduction in neural tube defects) on its own.
2. Most pregnant women do not have a prior history of giving birth to a baby with a neural tube defect and it was important to see - as far as was possible - whether the positive effects of folate applied in this group.
3. There was no heterogeneity across the four trials in any of the major outcomes we were reporting: neural tube defects, miscarriage, ectopic pregnancy, twinning, heart defects, and orofacial clefts.

4. Where there was some evidence of heterogeneity across the trials (for example in limb reduction defects, all other, non-specified, birth defects and in the frequency of conception), the trial in women having their first child had slightly better outcomes in that there were fewer limb reduction defects, fewer instances of all other (non-specified) birth defects and slightly more conceptions, although none of these differences was statistically significant.

(Summary of response from Judith Lumley, November 2006)

Contributors

Mark Selinger

POTENTIAL CONFLICT OF INTEREST

L Watson and M Watson are co-authors of one of the trials in this review.

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Iain Chalmers originated the initial review of this topic in the Oxford Database of Clinical Trials. Lesley Kumiega assisted with information retrieval in 1995-1996. Mona Saleh (then a medical student at the University of Calgary) made a substantial contribution to updating the review in 1996.

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* Indicates the major publication for the study

T A B L E S**Characteristics of included studies**

Study	Czeizel 1994
Methods	A randomised trial of periconceptual supplementation with multivitamins including folic acid (0.8 mg) (MF) or a trace element (P) to reduce the occurrence of neural tube defects.
Participants	Women attending the Hungarian Optimal Family Planning programme (HOFPP) who volunteered to take part, were not currently pregnant, and who conceived within 12 months of ceasing contraception. In the first 2 years of HOFPP women also had to be < 35 years, and not to have had a prior pregnancy except a prior induced abortion. 7905 women approached, 140 refused; 5502 had a confirmed pregnancy (2819 randomised to MF and 2683 randomised to P) and 49 of these (26 MF, 23 P) were lost to follow-up, leaving 2793 (MF) and 2660 (P).

Characteristics of included studies (Continued)

Interventions	Intervention was provided from at least 28 days before conception to, continuing until at least the second missed menstrual period. The multivitamin with folate (MF) included 6000 IU vitamin A, 1.6 mg vitamin B1, 1.8 mg vitamin B2, 2.6 mg vitamin B6, 4.0 mcg vitamin B12, 100 mg vitamin C, 500 IU vitamin D, 15 mg vitamin E, 19 mg nicotinamide, 10 mg Ca-pantothenate, 0.2 mg biotin, 0.8 mg folic acid, 125 mg calcium, 125 mg phosphorus, 100 mg magnesium, 60 mg iron 1 mg copper, 1 mg manganese and 7.5 mg zinc. The placebo (P) included 7.5 mg vitamin C, 1 mg copper, 1 mg manganese and 7.5 mg zinc.
Outcomes	Neural tube defects, other birth defects, miscarriage, ectopic pregnancy, termination of pregnancy, livebirths, stillbirths, multiple gestation. Sub-group data on sexual activity, first trimester symptoms.
Notes	Country: Hungary 1984-April 1992 with follow-up to April 1993. Because of serial publication of the study the totals change in later papers.
Allocation concealment	B – Unclear

Study **Kirke 1992**

Methods	A randomised trial comparing three supplements - multivitamins alone (M), folic acid alone (F) and multivitamins + folic acid (MF) - to prevent neural tube defects in families who had already had an affected child.
Participants	Women with a previous child who had an NTD (defined as anencephalus, iniencephalus, encephalocele or spina bifida aperta), defined from case registers of participating hospitals, who were not pregnant but were planning a further pregnancy, were eligible and invited to take part. 435 approached, 81.4% randomised (n = 354), 75 withdrew later and 16 were not pregnant leaving 263. The four withdrawals were in order to take Pregnavite Forte F. Three women could not be contacted for compliance measures and were lost to follow-up. The randomised groups were comparable in terms of maternal age, marital status, % in social classes 5 and 6, and prior obstetric history. Exclusion criteria: impaired absorption from the gastrointestinal tract.
Interventions	Tablets were originally prepared by Beecham and Glaxo to be white and indistinguishable. After 1 year only commercial preparations were provided. The MF tablet (Pregnavite Forte F) was purple and the others (M and F) were white. F tablets gave a daily dose of 0.36 mg/day M and MF tablets gave 4000 IU vitamin A, 400 IU calciferol, 1.5 mg thiamine hydrochloride, 1.5 mg riboflavine, 1 mg pyridoxine hydrochloride, 15 mg nicotinamide, 40 mg ascorbic acid, 480 mg calcium phosphate, and 252 mg ferrous sulphate. Compliance was assessed by tablet counts and blood tests (no data in this paper). Stability of M, MF and F tablets were assessed regularly by Glaxo and Hoffman La Roche.
Outcomes	Presence of a neural tube defect, other birth defects, livebirths, stillbirths, miscarriages, ectopic pregnancies, multiple gestation.
Notes	Sample size was planned to detect the reduction of NTDs in informative pregnancies from 5% to 1% at n = 462 (154 x 3). Unanticipated declines in the prevalence at birth of NTDs and in the number of births at participating hospitals led to premature closure of recruitment in late 1987, with follow-up to 1990. Data on 116 women already pregnant at the time of recruitment is also provided. Country: Republic of Ireland, 1981-1990.
Allocation concealment	A – Adequate

Study **Laurence 1981**

Methods	Randomised trial of folate supplementation before conception in women who had previously had a child with a neural tube defect and who were assessed as having a poor diet, or a diet high in fat and refined carbohydrates.
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Characteristics of included studies (Continued)

Participants	Women identified from multiple record sources as having had a child with an NTD (defined here as anencephalus, encephalocele or spina bifida cystica) between 1954 and 1969, and were < 35 years (n = 905) were invited to participate if they had a poor diet. 111 were randomised and had a subsequent pregnancy.
Interventions	Twice daily tablet of folic acid 2 mg from the time of stopping contraception. Measurement of compliance by tablet history and serum folate > 10 mcg/L at 6th to 9th week of gestation in the folic acid group: 16/60 were non-compliers.
Outcomes	Neural tube defect in subsequent pregnancy.
Notes	Country: Wales (UK) Prevalence at birth of NTDs in this population 1954-1969 was 7 per 1000. There are no details of the dietary analysis but a quarter of participants were graded as having an inadequate diet and an further 37% as having a fair diet.
Allocation concealment	B – Unclear

Study **MRC 1991**

Methods	A multicentre, multi-country, randomised double-blind trial with a factorial design and sequential analysis to determine whether supplementation with folic acid or a mixture of multivitamins in the periconceptional period would reduce the recurrence of neural tube defects. There was stratification by enrolling centre.
Participants	Women who had a previous pregnancy affected by a neural tube defect, were planning another pregnancy and not already taking supplements, were recruited from 33 centres in the United Kingdom, Hungary, Israel, Australia, Canada, the former USSR, and France (n = 1817). Exclusions were women whose affected child had Meckel's syndrome (autosomal dominant), and those with epilepsy. 1195 had an informative pregnancy before the trial was stopped, early.
Interventions	Prior to starting, women were given a printed leaflet: no one could enrol without a week to consider the decision. Capsules were for once daily treatment in one of four groups: folic acid 4 mg + di- calcium phosphate + 120 mg ferrous sulphate (F); multivitamins = 4000 IU vitamin A, 400 IU calciferol, 1.5 mg thiamine hydrochloride, 1.5 mg riboflavine, 1 mg pyridoxine hydrochloride, 15 mg nicotinamide, 40 mg ascorbic acid + the calcium and ferrous sulphate (M); folic acid + multivitamins as specified above (MF); the calcium and ferrous sulphate only (P). No special dietary advice was given. Women attended every 3 months for additional supplies and at the 12th week of pregnancy.
Outcomes	Neural tube defect, other birth defects, spontaneous abortion, ectopic pregnancy termination of pregnancy, livebirth, stillbirth, multiple pregnancy. Other papers report blood folate and zinc data.
Notes	Countries: United Kingdom, Hungary, Israel, Australia, Canada, the former USSR, and France. The planned sample size was 2000. The stopping rule (guideline only) had an alpha of 0.05 and a beta of 0.25 to identify a halving of the relative risk. Prenatal diagnosis of an affected pregnancy was available in all participating centres. The 4 groups were comparable in terms of maternal age, outcome of previous pregnancies and social class. Women remained in the study until they had an 'informative' pregnancy: one where the presence (or not) of an NTD could be confirmed. Confirmation of probable NTDs was subject to independent corroboration.
Allocation concealment	A – Adequate

Study **Watson 1999**

Methods	A community randomised trial.
Participants	Women who were aged between 15 and 44 years.
Interventions	Communities randomised to printed information recommending folate intake to reduce the risk of NTDs.

Outcomes	Women aware of the association between folate and spina bifida.
Notes	Country: Australia.
Allocation concealment	A – Adequate
F = folic acid alone MF = multivitamins and folic acid P = placebo (trace elements) HOFPP = Hungarian Optimal Family Planning programme IU = international unit NTD = neural tube defect	

Characteristics of excluded studies

Study	Reason for exclusion
Ulrich 1999	1. Miscarriages, including late miscarriages were excluded. 2. Only 16.6% were treated with folic acid prior to the last menstrual period.

ADDITIONAL TABLES

Table 01. Dissemination trial: % women aware of folate/NTD association

Study ID	Pre-intervention %	Post-int control	Post-int intervent	OR	95% Conf Interval
Watson 1999	12.4	15.8	19.8	1.37	1.33-1.42

ANALYSES

Comparison 01. All trials

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	4	6425	Relative Risk (Random) 95% CI	0.28 [0.13, 0.58]
02 Miscarriage	3	7600	Relative Risk (Random) 95% CI	1.12 [0.98, 1.29]
03 Ectopic pregnancy	3	7600	Relative Risk (Random) 95% CI	1.09 [0.47, 2.55]
04 Stillbirth (Fetal death)	3	7600	Relative Risk (Random) 95% CI	0.78 [0.34, 1.78]
05 Multiple gestation	3	6241	Relative Risk (Random) 95% CI	1.40 [0.93, 2.11]
06 Limb reduction defects	3	6314	Relative Risk (Random) 95% CI	0.59 [0.04, 8.34]
07 Conotruncal heart defects	3	6220	Relative Risk (Random) 95% CI	0.74 [0.16, 3.32]
08 Orofacial clefts	3	6314	Relative Risk (Random) 95% CI	0.76 [0.24, 2.37]
09 Other birth defects	3	6219	Relative Risk (Random) 95% CI	0.76 [0.38, 1.51]
10 Conception	3	10076	Relative Risk (Random) 95% CI	1.02 [0.97, 1.07]
11 Nausea, vomiting and vertigo	1	997	Relative Risk (Random) 95% CI	0.46 [0.26, 0.81]

Comparison 02. Occurrent neural tube defects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	1	4862	Relative Risk (Random) 95% CI	0.07 [0.00, 1.32]

Comparison 03. Folate prevention of recurrent neural tube defects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	3	1563	Relative Risk (Random) 95% CI	0.31 [0.14, 0.66]

Comparison 04. Multivitamin prevention of recurrent neural tube defects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	1	602	Relative Risk (Random) 95% CI	0.61 [0.26, 1.45]

Comparison 05. Folate vs multivitamin prevention of recurrent neural tube defects

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	2	774	Relative Risk (Random) 95% CI	0.27 [0.07, 1.08]

Comparison 06. Multivitamin vs Folate/multivitamin prevention of recurrent neural tube defect

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	2	773	Relative Risk (Random) 95% CI	2.05 [0.67, 6.26]

Comparison 07. Folate vs Folate/Multivitamin prevention of recurrent neural tube defect

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Neural tube defect	2	765	Relative Risk (Random) 95% CI	0.49 [0.09, 2.68]

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *Folic Acid; Neural Tube Defects [*prevention & control]; *Preconception Care; Pregnancy Outcome; *Vitamins

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects
Authors	Lumley J, Watson L, Watson M, Bower C
Contribution of author(s)	Judith Lumley and Carol Bower developed the protocol. Lyn Watson and Max Watson abstracted the data. All four reviewers have subsequently contributed fully to writing the review, updating the review and responding to comments from peer reviewers and from consumers.
Issue protocol first published	1998/2
Review first published	1998/4
Date of most recent amendment	15 November 2006

Date of most recent SUBSTANTIVE amendment	29 April 2001
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	06 March 2001
Date authors' conclusions section amended	29 April 2001
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DOI	10.1002/14651858.CD001056
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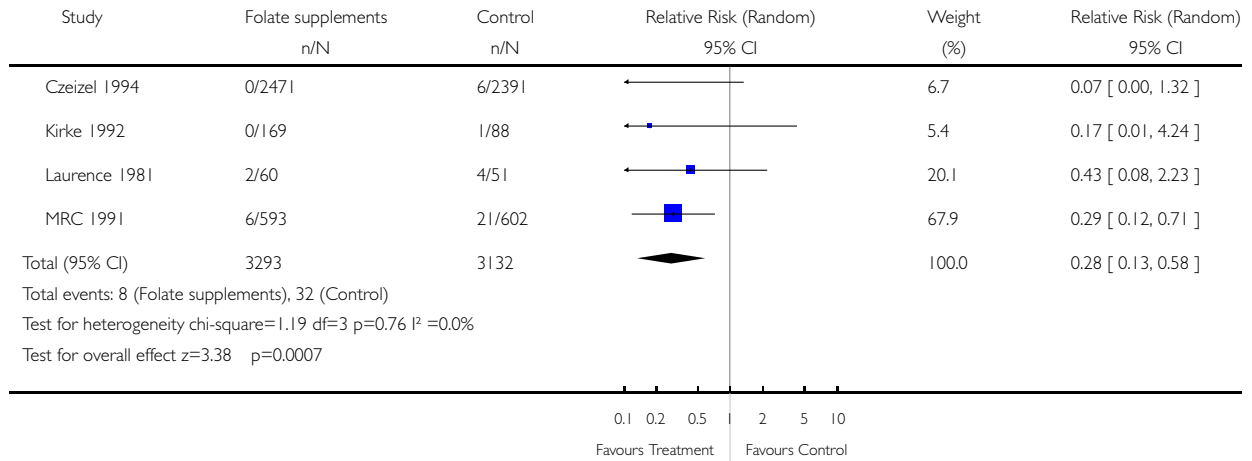
GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 All trials, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 01 Neural tube defect

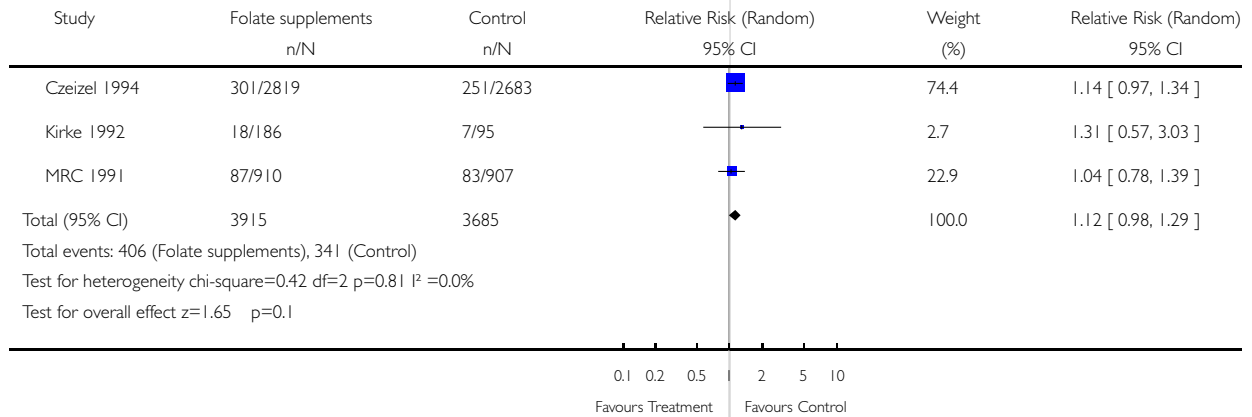


Analysis 01.02. Comparison 01 All trials, Outcome 02 Miscarriage

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 02 Miscarriage

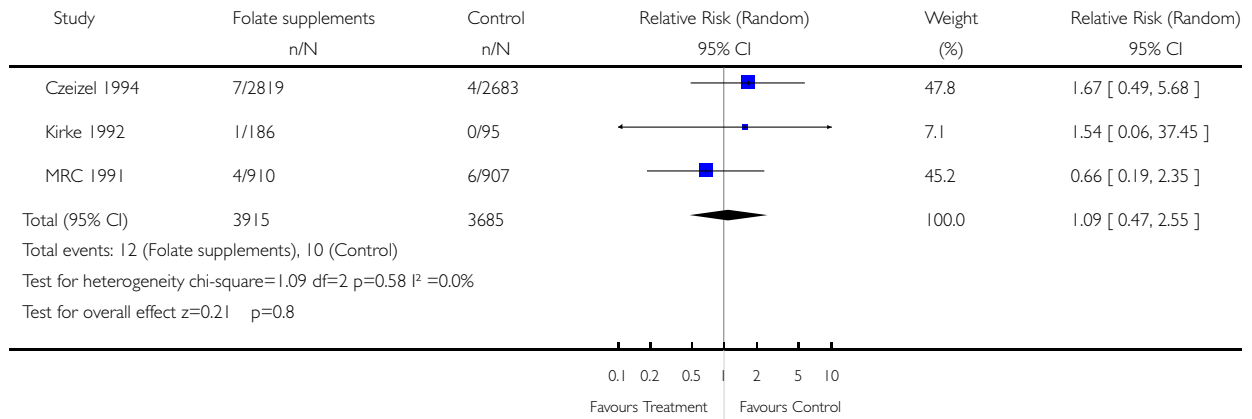


Analysis 01.03. Comparison 01 All trials, Outcome 03 Ectopic pregnancy

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 03 Ectopic pregnancy

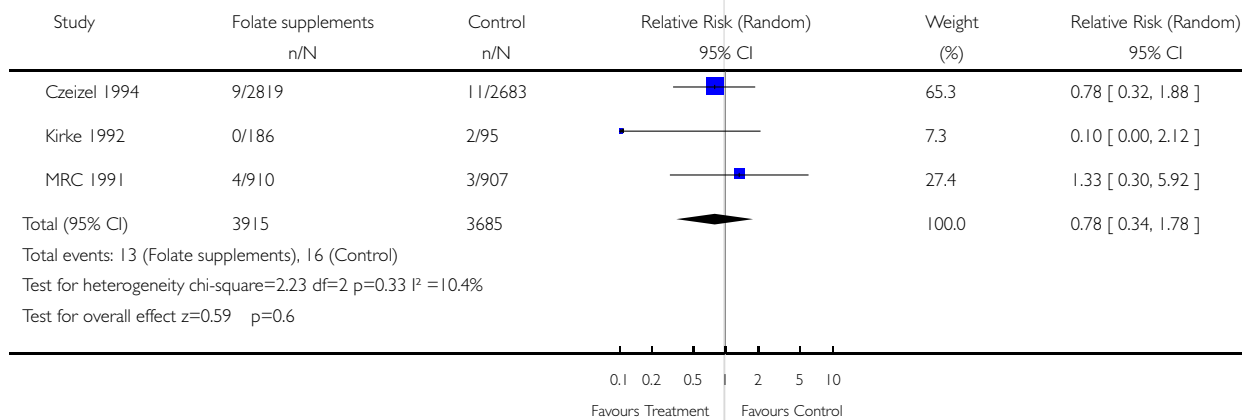


Analysis 01.04. Comparison 01 All trials, Outcome 04 Stillbirth (Fetal death)

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 04 Stillbirth (Fetal death)

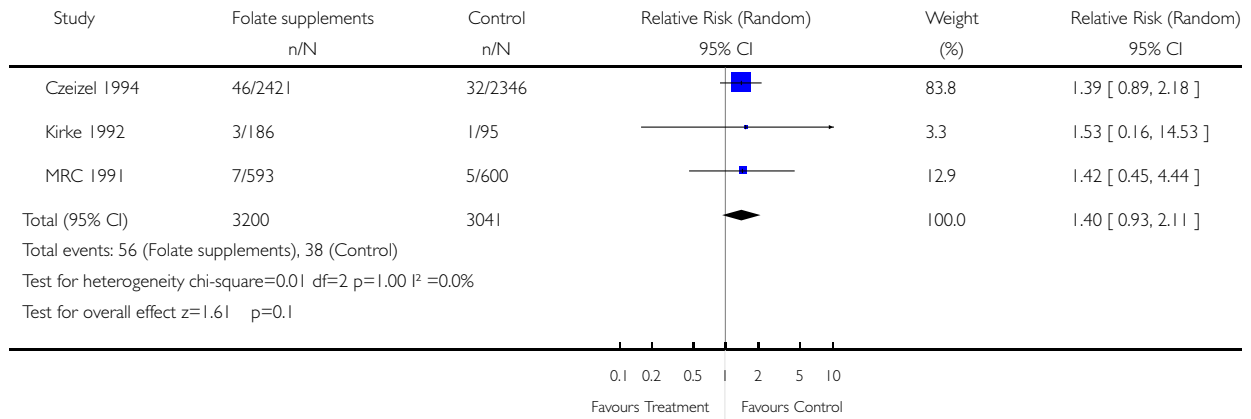


Analysis 01.05. Comparison 01 All trials, Outcome 05 Multiple gestation

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 05 Multiple gestation

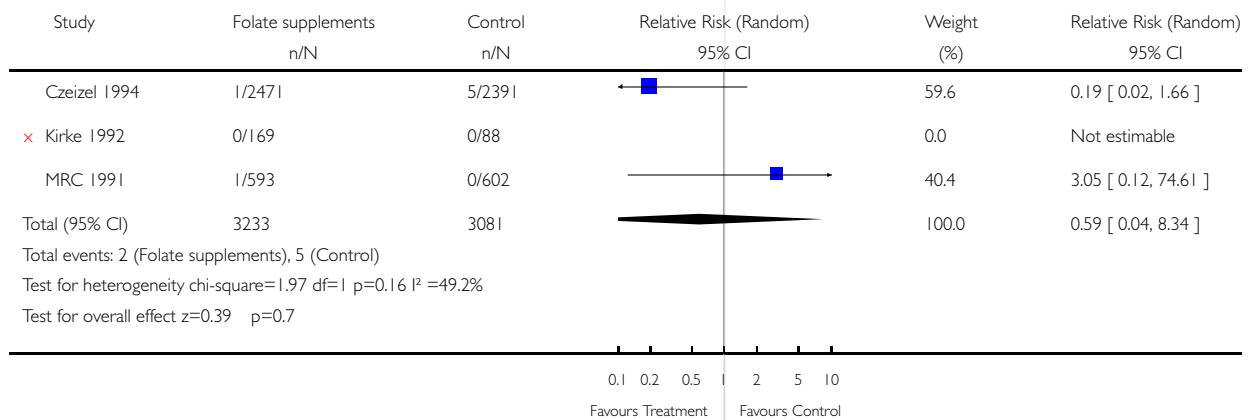


Analysis 01.06. Comparison 01 All trials, Outcome 06 Limb reduction defects

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 06 Limb reduction defects

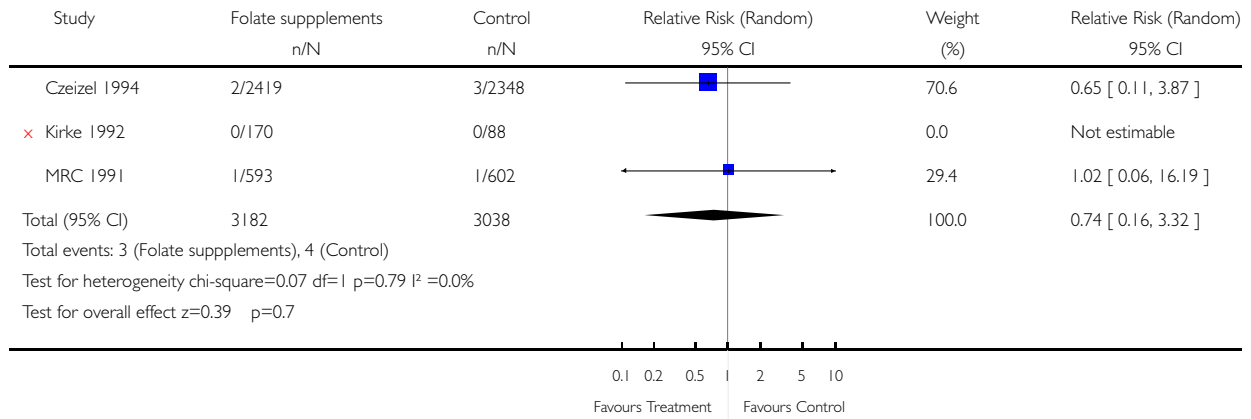


Analysis 01.07. Comparison 01 All trials, Outcome 07 Conotruncal heart defects

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 07 Conotruncal heart defects

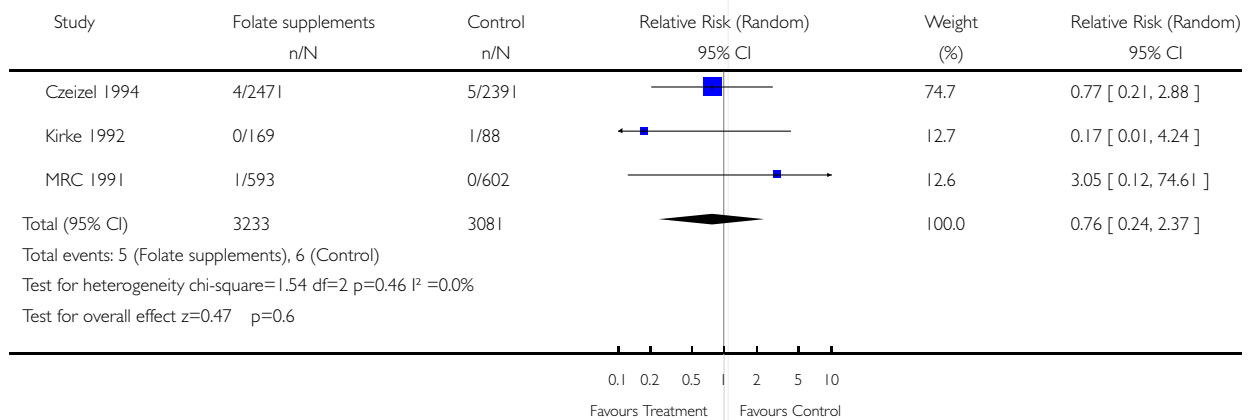


Analysis 01.08. Comparison 01 All trials, Outcome 08 Orofacial clefts

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 08 Orofacial clefts

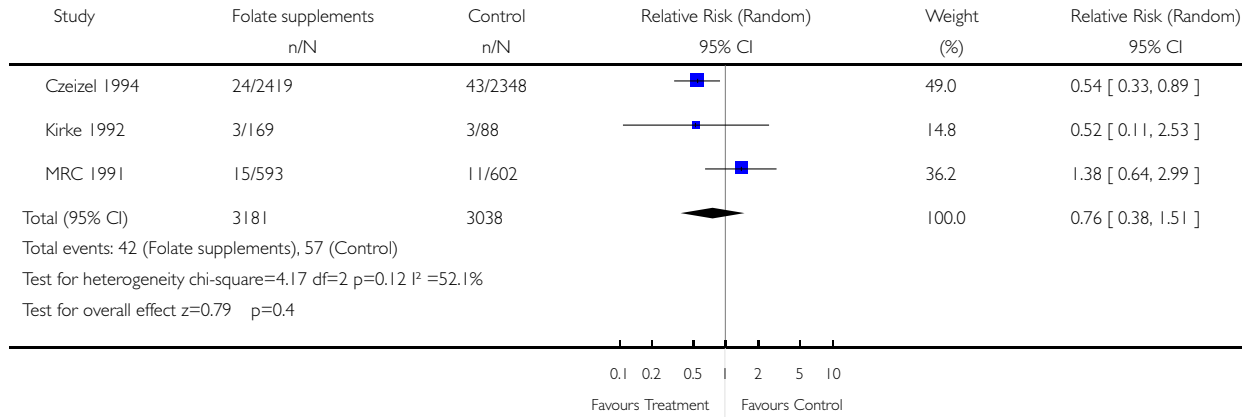


Analysis 01.09. Comparison 01 All trials, Outcome 09 Other birth defects

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 09 Other birth defects

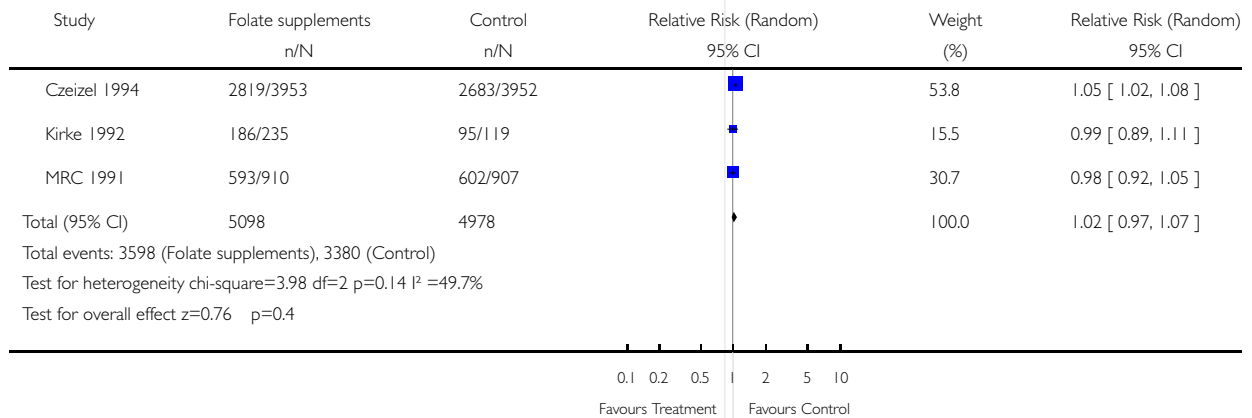


Analysis 01.10. Comparison 01 All trials, Outcome 10 Conception

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 10 Conception

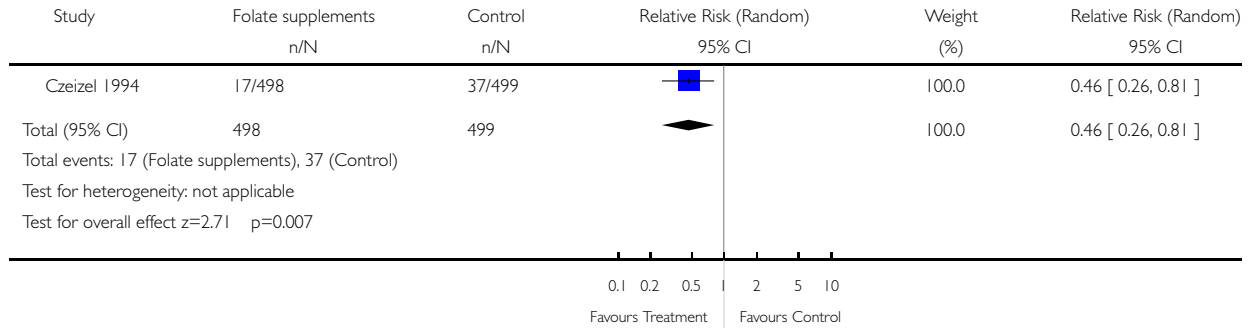


Analysis 01.11. Comparison 01 All trials, Outcome 11 Nausea, vomiting and vertigo

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 01 All trials

Outcome: 11 Nausea, vomiting and vertigo

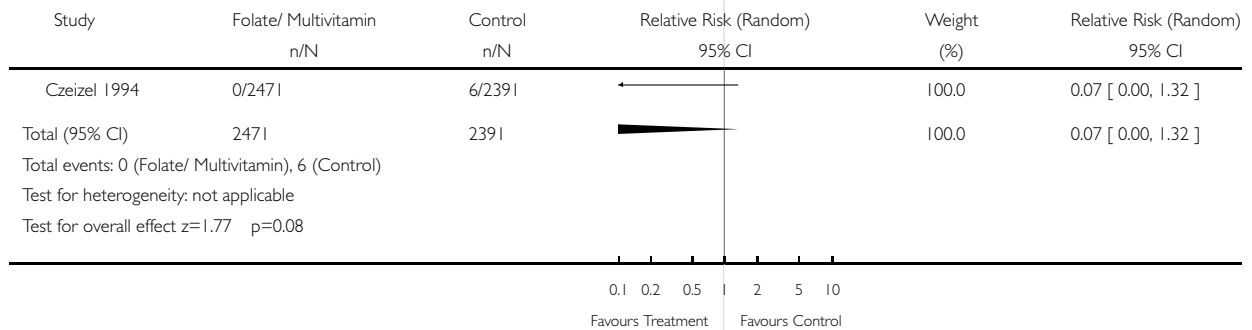


Analysis 02.01. Comparison 02 Occurrent neural tube defects, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 02 Occurrent neural tube defects

Outcome: 01 Neural tube defect

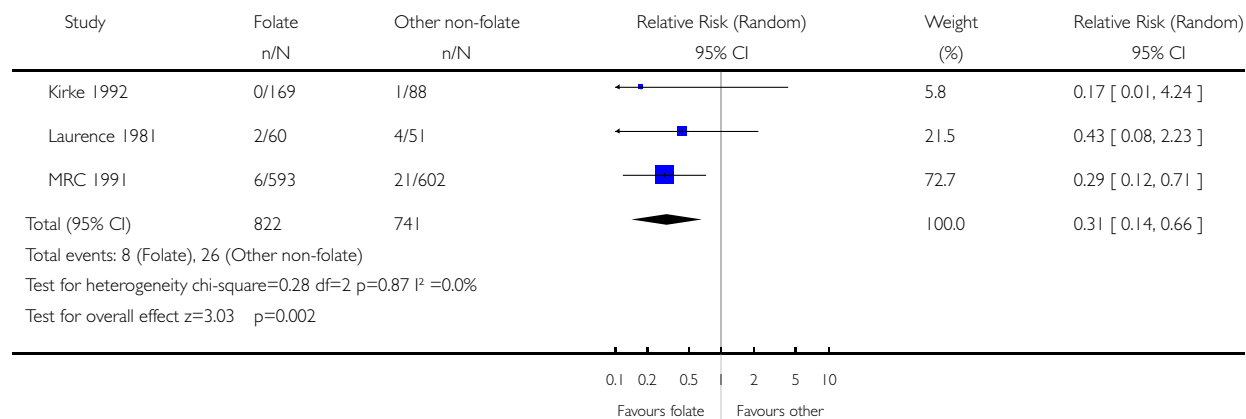


Analysis 03.01. Comparison 03 Folate prevention of recurrent neural tube defects, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 03 Folate prevention of recurrent neural tube defects

Outcome: 01 Neural tube defect

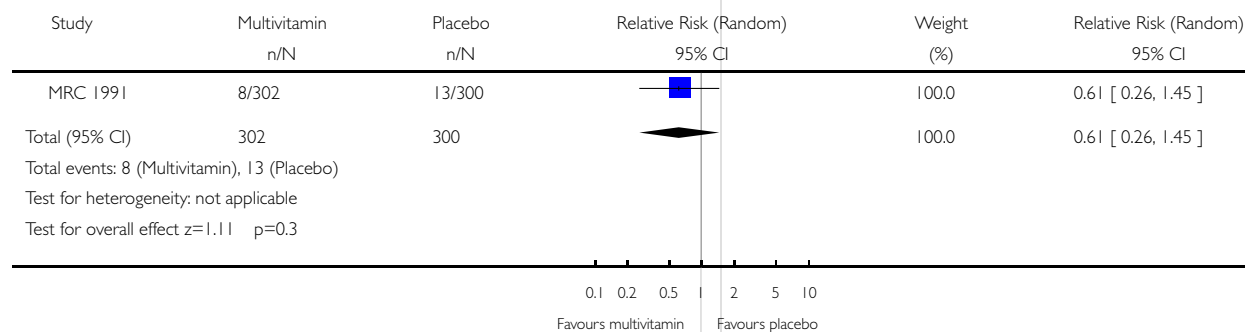


Analysis 04.01. Comparison 04 Multivitamin prevention of recurrent neural tube defects, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 04 Multivitamin prevention of recurrent neural tube defects

Outcome: 01 Neural tube defect

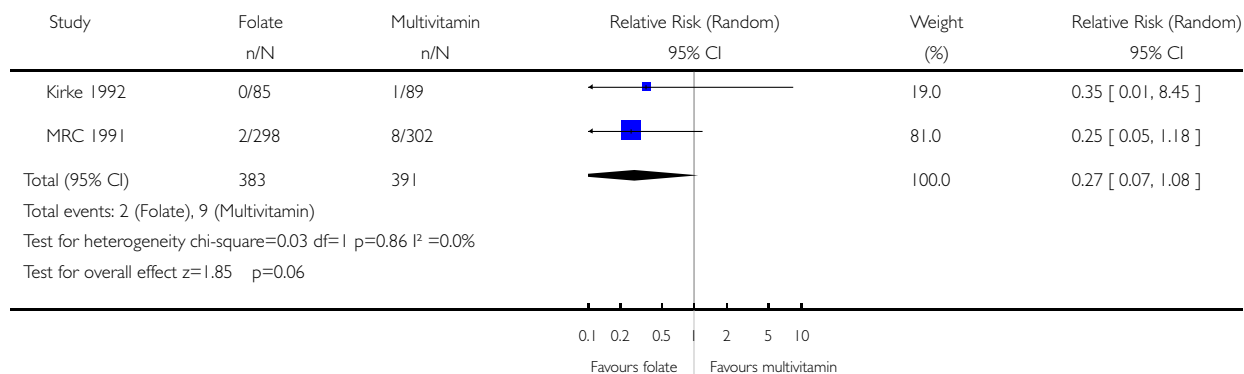


Analysis 05.01. Comparison 05 Folate vs multivitamin prevention of recurrent neural tube defects, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 05 Folate vs multivitamin prevention of recurrent neural tube defects

Outcome: 01 Neural tube defect

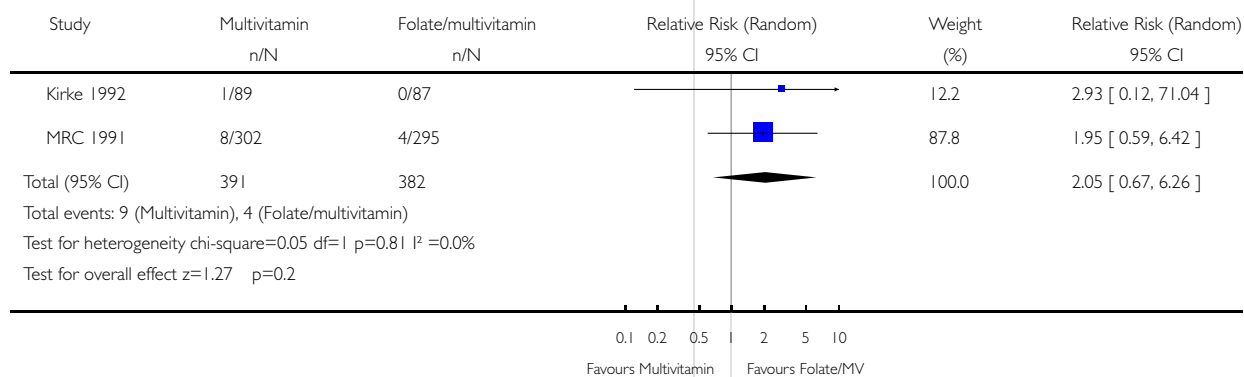


Analysis 06.01. Comparison 06 Multivitamin vs Folate/multivitamin prevention of recurrent neural tube defect, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 06 Multivitamin vs Folate/multivitamin prevention of recurrent neural tube defect

Outcome: 01 Neural tube defect



Analysis 07.01. Comparison 07 Folate vs Folate/Multivitamin prevention of recurrent neural tube defect, Outcome 01 Neural tube defect

Review: Periconceptual supplementation with folate and/or multivitamins for preventing neural tube defects

Comparison: 07 Folate vs Folate/Multivitamin prevention of recurrent neural tube defect

Outcome: 01 Neural tube defect

