NICE Maternal and Child Nutrition programme

Review 1: The effectiveness of public health interventions to promote nutrition of pre-conceptional women

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A review prepared for NICE by:

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1. Executive Summary

This rapid review examines the effectiveness of public health interventions provided to women (of childbearing age; pre-conceptional or peri-conceptional) to improve nutrition and health outcomes particularly folic acid/folate use and awareness.

1.1. Key questions

This rapid review answered five key questions:

1. What interventions are effective in increasing knowledge of the recommended intake of folate and folic acid among women of child bearing age who are planning a pregnancy or might become pregnant?

2. What interventions are effective in increasing uptake of folic acid supplements in non-pregnant women of child bearing age who are planning a pregnancy or might become pregnant?

3. What interventions are effective in increasing dietary folate in women of child bearing age who are planning a pregnancy or might become pregnant?

4. What interventions are effective in increasing health professionals' knowledge and awareness of the recommendations for folate and folic acid in women of child bearing age who are planning a pregnancy or might become pregnant?

5. What interventions (other than those about folate or folic acid) improve nutritional status of women of child bearing age who are planning a pregnancy or might become pregnant?

The literature search was conducted in June 2006 and updated in February 2007 using a stepped approach. Initially, a worldwide search was conducted to identify relevant systematic reviews (SRs) published during 1995 or onwards, followed by searches for randomised controlled trials (RCTs) conducted in developed countries and other study types conducted in the UK published during 1990 or onwards. A total of 5015 citations were independently screened by two reviewers, and full paper copies of 24 systematic reviews, 47 randomised controlled trials and 37 UK studies of any type were obtained and also independently assessed. In total, 12 studies met the inclusion criteria (two SRs, four RCTs published in five papers and six UK studies of any type.

1.2. Summary of evidence found

Key question 1: **What interventions are effective in increasing knowledge of the recommended intake of folate and folic acid among women of child bearing age who are planning a pregnancy or might become pregnant?**

Few studies evaluated methods to increase knowledge about the recommended intake of folate and folic acid. One cluster randomised trial (1+) conducted in Australia found that a significantly higher percentage of women of child-bearing age who received a community intervention involving the dissemination of printed information were aware of the importance of folate compared to women living in areas without the information – although general awareness significantly increased in both areas (Watson 1999; 2001). One media campaign conducted in the UK (2+) demonstrated that this type of intervention effectively increased awareness among women of child bearing age about the benefits of folic acid supplements (HEA, 1998).

In addition, a UK survey (3-) conducted in the 1990's indicated that there was a general lack of knowledge for the need for folic acid before pregnancy in both women and health professionals (Pearson, 1996).

Key question 2: **What interventions are effective in increasing uptake of folic acid supplements in non-pregnant women of child bearing age who are planning a pregnancy or might become pregnant?**

A SR (2+) reported that mass media campaigns conducted in developed countries significantly increased peri-conceptional folic acid use, but in no study was the post campaign rate of folic acid use >50% (Ray, 2004). This SR also reported that risk factors for low pre-conception folic acid use included low levels of formal education, young maternal age, lack of a partner, immigrant status and unplanned pregnancy. A US based RCT (1+) demonstrated that brief counselling from a physician about the benefits of folic acid along with the provision of free folic acid supplements increased weekly, but not daily, folic acid supplement use in women (Robbins 2005).

In addition, a UK survey (3+) conducted in the 1990's found that few women took folic acid, and that the use of supplements was positively related to maternal age, education, social class and living with a partner (Mathews, 1998).

Key question 3**: What interventions are effective in increasing dietary folate in women of child bearing age who are planning a pregnancy or might become pregnant?**

Only one study of any relevance was found which was an RCT (1-) that reported that an energy restricted diet and increased consumption of breakfast cereals (fortified with folic acid) significantly increased serum folate in women in comparison to those with an energy restricted diet and increased consumption of vegetables (Ortega 2006).

In addition, a UK survey (3+) revealed that no women increased their consumption of folate-containing foods pre-conceptionally despite current folic acid recommendations (Elkin 2000).

Key question 4: **What interventions are effective in increasing health professionals' knowledge and awareness of the recommendations for folate and folic acid in women of child bearing age who are planning a pregnancy or might become pregnant?**

No SRs or RCTs were identified that addressed this question. One large before-and-after survey (2+) demonstrated that the UK HEA folic acid campaign increased the percentage of health professional who gave folic acid advice to women planning a pregnancy (HEA, 1998). The survey also found that many health professionals working in the UK in 1997 had gaps in their knowledge about the appropriate dosage and timing of folic acid for women.

In addition, a UK survey (3+) reported that pharmacists and medicine counter assistants would only provide folic acid advice if they knew their customers well, or if customers asked for advice (Anderson 2002). The participants thought that raising awareness among unknown customers was limited to leaflets, displays and posters.

Key question 5: **What interventions (other than those about folate or folic acid) improve nutritional status of women of child bearing age who are planning a pregnancy or might become pregnant?**

Very few studies were found that evaluated nutritional interventions in women of child bearing age; one SR and one RCT were found. The SR (2+) aimed to evaluate the effectiveness of interventions to promote healthy eating in women of childbearing age (Van Teijlingen 1998). However, only one study in this review specifically aimed to improve dietary knowledge in young women (Fine 1994 in Van Teijlingen 1998). This UK-based RCT reported the effectiveness of basic nutrition education on nutritional knowledge, however this study was found to have several methodological limitations. One RCT (1-) reported that multivitamin-mineral and single cell oil containing docosahexaenoic acid supplements (that included iron and folate) were effective in raising blood levels of iron and folate in postpartum women (Doyle 2001). A UK before-and-after study (2-) reported that counselling sessions alone did not improve nutritional intakes of women from a socially disadvantaged area of London (Doyle, 1999).

1.3. Conclusions

Pre-conception care has the potential to improve pregnancy outcomes for both mother and foetus but there was a lack of high quality studies that evaluated the link between the general nutritional status of women of childbearing age and nutrition/health outcomes.

Mass media campaigns have been successful in increasing folate awareness and/or the uptake of folic acid supplements. Effective campaigns included leaflets, newspaper and television announcements, telephone messages and personal letters to health professionals. The evidence although sparse suggests that interventions aimed at increasing dietary intake of folate-rich foods are unlikely to be effective.

1.4. References to included papers, and methodology checklist ratings

Key question 1: What interventions are effective in increasing knowledge of the recommended intake of folate and folic acid among women of child bearing age who are planning a pregnancy or might become pregnant?

	Reference	***Methodology checklist rating***
1	Watson MJ, Watson LF, Bell RJ et al. (1999) A randomized community intervention trial to increase awareness and knowledge of the role of peri-conceptional folate in women of child-bearing age. *Health Expectations* 2(4): 255-65. Watson M, Watson L, Bell R et al. (2001) The increasing knowledge of the role of peri-conceptional folate in Victorian women of child-bearing age: follow-up of a randomised community intervention trial. *Australian & New Zealand Journal of Public Health* 25(5): 389-95.	1+ (Cluster RCT)
2	Health Education Authority (1998) Changing Preconceptions: The HEA Folic Acid Campaign 1995-1998.	2+ (UK survey evaluating a public health campaign)
3	Pearson S, Dimond H, Ford F et al. (1996). A survey of pre-pregnancy nutritional knowledge in family planning clinics. *The*	3- (UK survey)

	British Journal of Family Planning 22: 92-4.	

Key question 2: What interventions are effective in increasing uptake of folic acid supplements in non-pregnant women of child bearing age who are planning a pregnancy or might become pregnant?

	Reference	***Methodology checklist rating***
4	Ray JG, Singh G, Burrows RF (2004) Evidence for suboptimal use of peri-conceptional folic acid supplements globally. *BJOG: an International Journal of Obstetrics and Gynaecology* 111: 399-408.	2+ (SR)
5	Robbins JM, Cleves MA, Collins HB 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.	1+ (RCT)
6	Mathews F, Yudkin P and Neil A (1999) Influence of maternal nutrition on outcome of pregnancy: Prospective cohort study. *British Medical Journal* 319 (7206): 339-343.	3+ (UK prospective cohort study)

Key question 3: What interventions are effective in increasing dietary folate in women of child bearing age who are planning a pregnancy or might become pregnant?

	Reference	***Methodology checklist rating***
7	Ortega RM, Lopez-Sobaler AM, Andres P et al (2006) Changes in folate status in overweight/obese women following two different weight control programmes based on an increased consumption of vegetables or fortified breakfast cereals. *British Journal of Nutrition* 96(4):712-8.	1- (RCT)
8	Elkin AC and Higham J (2000) Folic acid supplements are more effective than increased dietary folate intake in elevating serum folate levels. *BJOG: An International Journal of Obstetrics & Gynaecology* 107 (2): 285-9.	3+ (UK survey)

Key question 4: What interventions are effective in increasing health professionals' knowledge and awareness of the recommendations for folate and folic acid in women of child bearing age who are planning a pregnancy or might become pregnant?

	Reference	***Methodology checklist rating***
9	Health Education Authority (1998) Changing Preconceptions: The HEA Folic Acid Campaign 1995-1998.	2+ (UK survey)
10	Anderson C and Rajyaguru R (2002) The role of community pharmacists and medicines counter assistants in health promotion: Reflections from a folic acid campaign. *International Journal of Pharmacy Practice* 10 (1): 17-22.	3+ (UK interviews)

Key question 5: What interventions (other than those about folate or folic acid) improve nutritional status of women of child bearing age who are planning a pregnancy or might become pregnant?

	Reference	***Methodology checklist rating***
11	Van Teijlingen E, Wilson B, Barry N et al. (1998) Effectiveness of interventions to promote healthy eating in pregnant women and women of childbearing age: a review. *London: Health Education Authority Report No.: Health Promotion Effectiveness Reviews* 11.	2+ (SR)
12	Doyle W, Srivastava A, Crawford MA et al. (2001) Inter-pregnancy folate and iron status of women in an inner-city population. *British Journal Of Nutrition* 86(1): 81-7.	1- (RCT)
13	Doyle W, Crawford MA, Srivastava A et al. (1999). Interpregnancy nutrition intervention with mothers of low-birthweight babies living in an inner city area: a feasibility study. *Journal of Human Nutrition and Dietetics* 12 (6): 517-27.	2- (UK before-and-after study)

2. Evidence statements

1. Evidence from one randomised community trial (Watson et al 1999 1+) and media campaign (Health Education Authority 1998 2+) conducted in developed countries to promote the uptake of folic acid supplements using advertising leaflets and promotional material, were effective in increasing awareness among women of child bearing age about the benefits of folic acid supplements.

2. Evidence from one systematic review (Ray et al 2004 2+) that included studies on interventions and media campaigns conducted in developed countries to promote the uptake of folic acid supplements using advertising, leaflets and promotional material reports that these campaigns were effective in increasing the proportion of women of child bearing age that regularly take folic acid supplements.

3. A large proportion of women of child bearing age who are planning a pregnancy or may become pregnant do not regularly take folic acid supplements. Evidence from one systematic review (Ray et al 2004 2+) that included 30 studies that reported risk factors for low pre-conception folic acid use found that low levels of formal education, young maternal age, lack of a partner, immigrant status and unplanned pregnancy are associated with lower odds of using folic acid around the time of conception.

4. Evidence from a RCT (Robbins et al 2005 1+) based on a southern population in the USA who received brief counselling from a physician about the benefits of folic acid along with the provision of free folic acid supplement tablets found that this was effective in increasing weekly folic acid supplement use.

5. There is evidence from a large survey (Health Education Authority 1998 2+) of health professionals working in England that folic acid advice is not perceived by them as being part of general health advice for women of child bearing age. The survey also found that many health professionals working in England have gaps in their knowledge about the appropriate dosage and timing of folic acid for women.

3. Background

There has been increasing recognition that achieving a healthy pregnancy outcome is strongly influenced by a woman's health status, lifestyle and history prior to conception (Korenbrot et al. 2002). Thus the development of pre-conception care that promotes health and prevents disease in women of reproductive age is also important to improve health outcomes. Indeed, folic acid advice is for all women, not just those planning a pregnancy, given that approximately 50% of pregnancies are planned, with as few as 25% of pregnancies planned among teenagers.

The National Service Framework for Children, Young People and Maternity Services Standard 11: Maternity Services (Department of Health, 2004) outlines:

Parents who are fit and healthy at the start of pregnancy generally have healthier babies. About half of pregnancies in the United Kingdom are unplanned and some women may delay seeking advice once they know they are pregnant, for a variety of reasons.

Prospective parents do not currently have easy access to information, such as the importance of folic acid supplementation prior to conception and ensuring rubella immunity, as rubella infection in the first eight to ten weeks of pregnancy results in fetal damage in up to 90% of infants.

Some women and prospective parents need specialist pre-conception advice, information and support, including:

- Women who have conditions treated with medicines that may harm the unborn baby need advice about changes in their medications prior to pregnancy; such conditions include epilepsy, schizophrenia, hypertension and bi-polar affective disorders;
- Women with a condition such as heart disease, a history of embolism, epilepsy or diabetes will need information and advice to ensure that their treatment is optimised, about managing their health before conception and during pregnancy, and
- Prospective or existing parents with a family history of a genetic disorder, and those who are concerned about familial disease or disabilities.

There are significant risks to the health, and life, of a baby if the mother smokes. These include the risk of miscarriage, premature birth and stillbirth, of placental abnormalities, low birthweight and, after birth, sudden infant deaths. It is estimated that about one third of all perinatal deaths in the UK are caused by smoking. There is also a significant risk to fetal development with women misusing drugs or alcohol.

Standard 11 states that:

All NHS maternity care providers, Primary Care Trusts and Local Authorities ensure that:

- Local multi-agency health promotion arrangements include health promotion for pregnancy;
- Campaigns and materials are targeted towards women in groups and communities who under-use maternity services or who are at greater risk of poor outcomes

Specific pre-conception services are available within the maternity care network and publicised for all women and their partners who require specialist advice before becoming pregnant, because of pre-existing medical or familial conditions;

The maternity care network works closely with primary health care providers, family planning and sexual health services to identify women with pre-existing medical or familial conditions who may become pregnant and ensure they have pre-pregnancy access to specialist advice should they plan to become pregnant, or appropriate contraception if they do not, and

All pregnant women and their partners who smoke receive clear information about the risks of smoking and the support available to them to stop e.g. the NHS Stop Smoking Service as part of the broader strategy of improving the health of the population (a Department of Health national target).

The National Service Framework also requires that local health promotion arrangements need to include the provision of the following information for parents:

- What becoming a parent might be like and the impact on wider family/ adult relationships.
- The importance of:
  a) pre-conceptional folic acid;
  b) minimising intake of alcohol;
  c) not using recreational drugs;
  d) not smoking during pregnancy and having a smoke-free environment;
  e) pre-pregnancy rubella immunisation, and
  f) seeing a healthcare professional as early in pregnancy as possible.

The challenge is that few women seek care prior to conception and many women have unintended pregnancies or seek care too late in pregnancy for effective preventive care. It is estimated that approximately 30–50% of pregnancies in England and Wales are unplanned, as are 75% of teenage pregnancies (Health Education Authority, 1998).

3.1. Pre-conceptional dietary advice

The Food Standards Agency (FSA) provides dietary advice for women planning a pregnancy (Food Standards Agency, 2005). This advice includes:

- Following a healthy, varied and balanced diet
- Consuming plenty of iron-rich and folate-rich foods
- Taking a folic acid supplement of 400 µg per day
- Limit their alcohol and caffeine intakes
- Avoid taking vitamin A supplements, or foods containing high levels of vitamin A (such as liver and liver products)
- Certain types of fish, such as shark, swordfish and marlin, should be avoided and to limit tuna intake due to possible contamination

3.2. Pre-conceptional folic acid

Folic acid is an artificial form of folate, the B vitamin naturally found in foods, such as green vegetables. Foods which are rich sources of folate (50 to 100 micrograms per serving) include cooked black eye beans and chick peas, granary bread, spring greens, kale, spinach, broccoli, and yeast extract. Medium sources of folate (15 to 50 micrograms per serving) include cooked lentils and kidney beans, baked beans, peas, orange juice, cabbage, eggs, cauliflower, courgettes and green peppers.

Folic acid has the same vitamin activity as natural folate and is used in dietary supplements and for the fortification of foods. Breads that are fortified with folic acid tend to contain about 90 micrograms per 2 slices. Breakfast cereals that are fortified with folic acid tend to contain about 100 micrograms per 30g serving.

3.3. Folic acid and neural tube defects

It is recognised that folic acid is of crucial importance both pre-and peri-conceptionally in protecting against neural tube defects (NTDs) in the developing foetus. The neural tube develops into the spine and NTDs occur when the brain and skull and/ or the spinal cord and its protective spinal column do not develop properly within the first four weeks after conception. The most common NTDs are anencephaly, which results in stillbirth or death soon after delivery, and spina bifida, which may lead to a wide range of physical disabilities, including partial or total paralysis.

The National Congenital Anomaly System (NCAS) collates NTD affected birth data for England and Wales. In 2002, NCAS data showed that of a total of 599,279 live births, there were 380 NTD affected pregnancies (6.3 per 1,000 births), 258 NTD reported terminations (4.3 per 1,000 births) and 122 NTD affected births (2.0 per 1,000 births) (Scientific Advisory Committee on Nutrition (SACN), 2005). However a limitation of NCAS data is an under-reporting of terminations (of between 34-56%), therefore in 2002 it has been estimated that there were an estimated 510-590 NTD affected pregnancies in England and Wales (SACN, 2005) and 551-631 NTD affected pregnancies in the UK.

There is now conclusive evidence from a number of randomised controlled trials that pre-conceptional supplementation with folic acid significantly reduces the risk of NTDs. The Department of Health (DH) (1992) recommends that all women who are planning a pregnancy are advised to take a daily supplement of folic acid (400 µg) prior to conception until the 12th week of pregnancy. Women with a history of neural tube defects are advised to see their GP to obtain prescribed dose of folic acid supplements of 4mg per day. Women are also advised to eat foods rich in folate. Obtaining the recommended amounts by diet alone is difficult. Furthermore, it may not be feasible for all women to follow the advice, as about a half of all pregnancies are unplanned (SACN, 2005).

There has been a secular decline in NTD births in the UK over the last three decades - well before awareness of the benefits of folic acid supplementation. The rate in 1997 was one tenth of the rate in the mid-1960s. General improvements in diet and social conditions may partially explain the fall. It has also been suggested that some of this decline may be due to antenatal screening and termination (one study estimated 40%).

3.3.1. Intakes of pre-conceptional folic acid

The Health Survey of England 2002 provides the most up-to-date information on the use of folic acid supplements, prior to and during pregnancy, by women of child bearing age. Information on folic acid supplements was collected prior to pregnancy from mothers who had planned their pregnancy, who comprised two-thirds of the interviewed sample.

Of the mothers who reported planning their pregnancy, over half (55%) reported taking their supplements or modifying their diet to increase folate intake. The proportion of mothers taking action to address folate intake increased with age from 32% of 16-24 year olds to 60% of those aged over 35 years (SACN, 2005).

All mothers were questioned about their supplement intake during pregnancy. Seventy nine percent of mothers reported an increase in their folate intake during pregnancy and this proportion increased with maternal age (SACN, 2005).

Furthermore, the Infant Feeding 2000 Survey, based on retrospective postpartum interviews of mothers found that 73% of mothers had taken folic acid supplements or modified their diets to increase their folate intake in early pregnancy. Information was not available on whether action had taken place pre/ post conception (SACN, 2005).

3.3.2. Dietary intakes of folate

Data from the National Diet and Nutrition Surveys (NDNS) of adults aged 19-64 years show that:

- Adult women mean daily intakes of folate was above the RNI (of 200 µg) at 292 µg. Less than 2% of women had intakes below the LRNI of 100 µg per day.
- Although the average folate intakes were greater than the RNI, 8% of women aged 19 to 24 years had red blood cell folate concentrations indicative of an increased risk of marginal status.
- The average red blood cell folate concentrations of women aged 19 to 24 years, 25 to 34 years and 35 to 49 years were 256 µg/ L, 314 µg/ L and 309 µg/ L respectively. This suggests that women of childbearing age in the UK have an intermediate risk of NTD-affected pregnancies. There is a higher incidence of NTD-affected pregnancies in England and Wales in younger women, which corresponds to the lower folate status in this group (SACN, 2005).
- For young people aged 4-18 years, mean daily intakes of folate was 197 µg for girls, above the RNI of 100-200 µg. Less than 3-4% of girls over 11 years of age had intakes below the LRNI of 100 µg per day.
- Nine percent of girls had red blood cell folate concentrations indicative of marginal status. No more than 1% of any age/ sex group had red cell folate concentrations indicating folate deficiency (SACN, 2005).

3.4. Bodyweight and fertility

It has now been established that fertility in women is affected by their percentage body fat, rather than absolute bodyweight. The average body fat content in women is 28% of bodyweight, and research has shown that a body fat content of at least 22% is necessary for normal ovulatory function and menstruation (Williamson, 2006).

Women who maintain a low bodyweight, who have suffered from eating disorders, or who diet regularly, often have irregular menstrual cycles and therefore take longer to conceive. Gaining weight restores fertility, however excessive stores of body fat can also impair fertility. Women with BMI over 30 kg/m2 take longer to conceive, compared with women with a lower BMI, even after adjusting for other factors such as menstrual irregularity (Zaadstra et al. 1993; Jensen et al. 1999; Bolumar et al. 2000).

The NICE clinical guideline *Fertility assessment and treatment for people with fertility problems* (2004) makes the following recommendations in relation to body weight:

- Women who have a body mass index of more than 29 should be informed that they are likely to take longer to conceive. (Grade B recommendation)

- Women who have a body mass index of more than 29 and who are not ovulating should be informed that losing weight is likely to increase their chance of conception. (Grade B)
- Women should be informed that participating in a group programme involving exercise and dietary advice leads to more pregnancies than weight loss advice alone. (Grade A)
- Women who have a body mass index of less than 19 and who have irregular menstruation or are not menstruating should be advised that increasing body weight is likely to improve their chance of conception. (Grade B)

3.4.1. Pre-pregnancy weight and birth outcome

It is recommended that women who are planning a pregnancy should attempt to reach a healthy bodyweight (Body Mass Index (BMI) of 20-25) before they become pregnant, as being overweight or obese, or underweight prior to conception is associated with an increased risk pf complications.

Mothers with a low BMI prior to and during pregnancy are at an increased risk of having a low birthweight infant (less than 2.5 kg). Being underweight is also associated with an increased risk of morbidity and mortality in the newborn infant and an increased risk of degenerative diseases in later life of the offspring (Williamson, 2006).

Being overweight or obese prior to and during pregnancy is associated with an increased risk of several complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and congenital defects. Obesity is also linked to a greater risk of abnormal labour and an increased likelihood of needing an emergency caesarean operation. The incidence of these complications appears to increase as the pre-pregnancy BMI increases, so women who are severely obese are at greatest risk of experiencing such complications (Williamson, 2006).

The Health Survey for England found that around two-thirds of women were either overweight or obese in 2004. Furthermore, 2.6% of women are classified as morbidly obese, with a BMI of over 40 kg/m (Department of Health, 2005).

3.5. Pre-conceptional nutrition and inequalities

3.5.1. Teenage pregnancy

The UK has one of the highest rates of teenage pregnancy in Europe, although rates have declined slightly since 1998. In England, the current teenage conception rate is 42.1 per 1000 girls aged 15-17 years. In 2003, 46% of under-18 conceptions led to legal terminations (Office for National Statistics, 2005). Studies have shown that teenage pregnancy is associated with lower gestational weight gain and an increased risk of low birthweight, pregnancy induced hypertension, pre-term labour, iron deficiency anaemia and maternal mortality.

Furthermore, teenage pregnancy occurs at a time when the maternal body already requires extra nutrients for growth and development, so there is potential competition for nutrients. It is possible that maternal growth and development may be compromised, with priority given to the developing foetus. It has also been suggested that there is a reduced flow of nutrients to the foetus in teenage pregnancy due to immature placental development (Williamson, 2006).

One nutrient of particular importance during teenage pregnancy is calcium, as a rapid increase in bone mass occurs during the adolescent years so the maternal skeleton

is still developing. Although some physiological adaptations take place, which may help to meet additional calcium requirements during pregnancy, teenage girls require more calcium than adults for bone development (Williamson, 2006). Iron intakes have been found to be below the LRNI in up to half of teenage girls in the UK, and many teenage girls have low iron stores, which is also of concern for unplanned teenage pregnancy.

Other inequality considerations for pre-conceptional nutrition include:

- Only 43% of mothers in the most socio-economically deprived areas were likely to increase folate intake pre or during pregnancy compared to 70% of mothers from the least socio-economically deprived areas (SACN, 2005).
- Furthermore, women at the greatest risk of NTD are the least likely to follow folic acid advice. Women from higher social groups were more than twice as likely to follow the advice to take pre-conceptional supplements (HEA 1998). Women over 25 years of age are much more likely to follow the advice than younger women.
- The NDNS data for adults shows those women in receipt of benefits had significantly lower folate intakes from foods than their peers (SACN, 2005).
- The National Audit Office found that obesity is more prevalent among lower socioeconomic and lower-income groups, with a particularly strong social class gradient among women (NAO, 2001).

3.6. References

Bolumar F, Olsen J, Rebagliato M, Saez-Lloret I, Bisanti L. (2000) Body mass index and delayed conception: a European multicenter study on infertility and subfecundity. *Am J Epidemiol*;151:1072–9.

Department of Health (1992) Folic acid and the prevention of neural tube defects. Report from an Expert Advisory Group. London: Department of Health.

Department of Health (2004) National Service Framework for Children, Young People and Maternity Services. London: Department of Health.

Department of Health (2005) *Health survey for England – trends*. London: Department of Health.

Food Standards Agency (2005) Trying for a baby (advice) http://www.eatwell.gov.uk/agesandstages/pregnancy/trybaby/

Health Education Authority (1998) *Changing pre-conceptions. Volume 2. the HEA folic acid campaign 1995–1998. Research Report*. London: Health Education Authority.

Jensen TK, Scheike T, Keiding N, Schaumburg I, Grandjean P. Fecundability in relation to body mass and menstrual cycle patterns. (1999) *Epidemiology*; 10:422–8.

Korenbrot, C. C., Steinberg, A., Bender, C. & Newberry, S. (2002). Pre-conception care: a systematic review. *Maternal and Child Health Journal*, 6 (2) 75-88.

Office for National Statistics (2005) Teenage conception statistics for England 1998-2003. In Health Services Quarterly. www.dfes.gov.uk

National Audit Office. (2001) *Tackling obesity in England*. London: The Stationery Office.

SACN (Scientific Advisory Committee on Nutrition) (2005) Folate and disease prevention (Draft report) www.sacn.gov.uk

Williamson, C. S. (2006) Nutrition in pregnancy. *Nutrition Bulletin*, 31, 28-59.

Zaadstra BM, Seidell JC, Van Noord PA, te Velde ER, Habbema JD, Vrieswijk B, *et al.* (1993) Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. *BMJ*; 306: 484–7.

4. Methodology

This rapid review addresses five questions which were modified from the NICE protocol which originally aimed to address the following three questions:

1) What nutrition interventions are effective in improving pregnancy outcomes in women of childbearing age?
2) What pre-conceptional and peri-conceptional nutrition interventions, undertaken by women planning a pregnancy, are effective in improving nutritional status and/or pregnancy outcome?
3) What interventions are effective in a) increasing dietary folate intake and status and b) increasing the uptake of folic acid supplements in women planning a pregnancy?

The changes made were to increase clarity and were not thought to affect the search strategy. This alteration was done at the request of NICE in response to the Programme Development Group (PDG), that being the committee responsible for producing the guidance.

An earlier version of this rapid review (September, 2004) included a number of studies not presented in this revised rapid review (e.g. studies on vitamin supplementation and pregnancy outcomes) (see Appendix B). It should be noted that in the UK there are recommended daily intakes of vitamins and minerals for women of all ages and when pregnant.

4.1. Literature Search

Kath Wright (Centre for Reviews and Dissemination, University of York) conducted the searches for this rapid review in June 2006, which were updated in February 2007. Initially, a scoping search was undertaken in order to direct and refine the final search strategy with input from the MCN-CC review team (AM and SEK).

All of the searches were conducted using a stepped approach to identify relevant systematic reviews (SRs), randomised controlled trials (RCTs), and non-randomised studies (cohorts, qualitative studies and surveys) published in the UK. A worldwide search of all the main databases in which nutrition intervention studies might be found was conducted to identify relevant systematic reviews (from 1995 onwards). Secondly, a worldwide search for randomised controlled trials (RCTs) was conducted (from 1990 onwards). Thirdly, a search for any other type of nutrition intervention study was undertaken but this search was restricted to studies undertaken in the UK and published from 1990 onwards. In addition as part of the NICE consultation process stakeholders and members of the Programme Development Group suggested papers that they believed should be screened for inclusion. These papers were screened but none were included in the review. The reasons for exclusion are reported in appendix B.

Studies not published in English were excluded from the review. A detailed report of the processes, databases, and search terms used in this rapid review are presented in Appendix C.

4.2. Selection of Studies for Inclusion

4.2.1. Participants

To be included in this rapid review, the studies had to evaluate women of childbearing age and/or women planning a pregnancy, or women around the time of conception. Adolescents/teenagers were included. Around ‘the time of conception’

was considered to be up to12 weeks pregnant. However, if studies reported that the intervention took place at a mean gestation of 12 to 13 weeks, they were included as well as interventions that took place during the 'first trimester'.

Where data were available, the review considered areas of deprivation including inner city areas, children from black and minority ethnic groups and children of mothers below the age of 18 years. Studies of participants for whom normal care was inappropriate were excluded from the review. This included women with established problems with alcohol.

4.2.2. Interventions

The review included all public health interventions that aimed to promote the nutrition/health of women of childbearing age, either planning a pregnancy or around the time of conception. These included, but were not limited to, the following interventions:

- Education programmes
- Educational literature
- Counselling
- Provision of free supplements
- Marketing and media campaigns
- Training of health professionals

4.2.3. Outcomes

The primary maternal outcomes of interest were:

- Dietary intake
- Changes in food choices
- Knowledge of recommended intake of folate and folic acid
- Intake of folic acid/folate
- Weight management and BMI

4.2.4. Study design

- Systematic reviews that include studies from developed countries
- RCTs conducted in developed country settings only
- Intervention studies of other designs and qualitative and quantitative surveys conducted in the UK

Note: In addition to the above NICE requested that data from eleven papers reporting studies that were not randomised control trials and were undertaken outside the UK were retrieved. These are not included as part of the systematic review process, but are considered to complement the evidence found and are described in Appendix E.

4.2.5. Selection of studies

Two reviewers independently screened titles and abstracts identified in the literature search. Full paper copies of potentially relevant studies were obtained and independently assessed for inclusion by two reviewers. Any disagreements regarding whether or not a paper met the inclusion criteria was achieved by consulting a third reviewer. A list of excluded SRs and RCTs with reasons for exclusion is presented in Appendix B.

4.2.6. Quality appraisal

All of the studies that met the inclusion criteria were critically appraised by two reviewers in accordance with criteria described in NICE (2006). A study was graded using a code '++', '+' or '-', based on the extent to which the potential sources of bias had been minimised. If there was any discrepancy in a grade given to a study by the two reviewers, the opinion of a third reviewer was sought. The NICE criteria and the methodology checklist used in this review are presented in Appendix D. It is noted that these grades reflect the quality of the author's reporting of their study.

4.2.7. Assessing applicability

Each included study was assessed to determine its applicability to UK settings. Notes on applicability are presented in the data extraction tables.

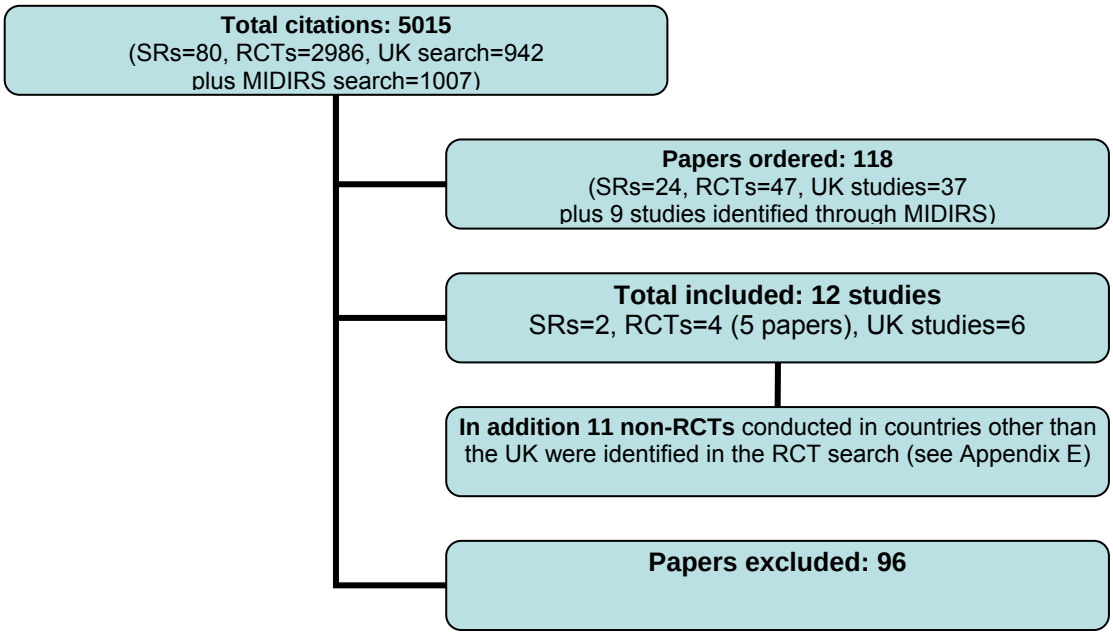
5. Summary of Findings

In total, 12 studies met the inclusion criteria (2 SRs and 4 RCTs published in 5 papers, and 6 UK studies of any type). Full references for the included studies are listed in Appendix A, and data extraction tables in Appendix F. Citations and reasons for exclusion of other SRs and RCTs are listed in Appendix B. A further eleven papers of non-UK studies were identified which are not included in the review since they were not SRs or RCTs but might be of interest to readers and these are summarised in Appendix E.

From 5015 titles and abstracts identified in the literature search, full paper copies of 118 studies were obtained (a number of these studies would have addressed questions not addressed in this updated rapid review., e.g. studies of vitamin supplementation and pregnancy outcomes).

Citations identified by the two searches are shown in the table below:

	SRs	RCTs	UK studies	MIDIRS	Totals
June 2006	65	2713	864	1007	4649
February 2007	15	273	78	-	366
Totals	80	2986	942	1007	5015



5.1. Key question 1: What interventions are effective in increasing knowledge of the recommended intake of folate and folic acid among women of child bearing age who are planning a pregnancy or might become pregnant?

No SRs were identified in our literature search that addressed this question. One cluster RCT (1+) evaluated the effects of an information campaign recommending folate intake to decrease the risk of neural tube defects (NTDs) (Watson et al 1999; 2001). In three out of six local government areas (LGAs) in Victoria, Australia, printed information (i.e. leaflets, posters and other materials) was disseminated in a range of locations where it was thought women of childbearing age would read it (e.g. grocery stores, schools, health centres). The LGAs were geographically isolated from each other, and study information was not distributed in the control areas. The number of women of childbearing age who were surveyed was 2403, sufficient to meet the power calculation requirements of the study. Before the intervention, 12.4% were aware of the association between folic acid and NTDs. After the intervention, a significant background increase in folate awareness (3.4%, p=0.02) was found, with an additional significant increase of 4.0% (p=0.04) in the intervention group (OR 1.37, 95% CI: 1.33-1.42). At the three-year follow-up, the significant difference between areas persisted, with an overall increased awareness of 30%. However, further folate-related health promotion activities had taken place since the intervention.

In addition, a before-and-after (2+) UK study evaluated the 'Health Education Authority Folic Acid Campaign' (HEA, 1998). This campaign included a range of media and public relations activities including leaflets, posters, television and magazine advertisements as well as provision of a free phone advice line. After three years (1995-98), there were large increases in awareness of the importance of folic acid in pregnancy, such that in 1998, 89% of women were reported to be aware of the importance, compared to 51% in 1995. It is not known, however, what part of this multi-intervention strategy had the most impact.

In addition to these studies, a UK cross-sectional survey (3-) was of potential interest. It was designed to assess peoples' knowledge of general nutritional guidelines and government directives about pregnancy nutrition for folate/folic acid, vitamin A and food borne infections (Pearson 1996). This survey was conducted in three large family planning clinics in Sheffield on a sample of never-pregnant clients (n=60) and staff (n=16). All staff and 93% clients were white. Twelve percent of clients and 69% of health professionals understood the need for folic acid before pregnancy. Given the date of this study, and the success of the 'Health Education Authority Folic Acid Campaign', the usefulness of this study to inform our research question is limited.

Strength and applicability of evidence

One cluster randomised trial conducted in Australia (Watson 1999) provides level 1+ evidence that women of child-bearing age who received a community intervention involving the dissemination of printed information resulted in a significantly higher percentage of folate awareness compared to women living in areas without the information – although general awareness significantly increased in both areas.

One media campaign conducted in the UK (HEA 1998) provides level 2+ evidence that this type of intervention effectively increases awareness among women of child bearing age about the benefits of folic acid supplements.

Reference	How does the structure and content of the intervention influence effectiveness?	Does effectiveness vary by gender, age, ethnicity, religious practices or social/ professional group of those receiving or delivering the intervention?	Does effectiveness vary with site/ setting or intensity/ duration of the intervention?	What are the views of those receiving and delivering the intervention?	Is there evidence of unintended or harmful effects?	Are there barriers to replication of effective interventions?
Watson 1999; 2001	The intervention period was just over 2 months and the evaluation that showed effectiveness of the intervention took place 1-2 months later The best-remembered information was that presented on the brief leaflet (one side of A5) The information about when to take folic acid was less well remembered. Where this information was printed is not reported No data on whether women, including pregnant women, were taking folic acid are presented,	Women under 25y had the lowest folate awareness and women 25-34y the highest awareness, and women in a professional occupation had higher awareness than those in other occupations, both before and after the intervention After the intervention, a smaller percentage of 15-24y women in the intervention group was folate-aware than before the intervention or among the post-intervention controls A written materials	Site/ setting: No Duration of the intervention did not vary	Four times as many women remembered seeing the leaflet than the poster or information kit. The leaflet was distributed mainly at supermarket checkouts	No	Effectiveness of the written information may depend on baseline levels of awareness Assessing baseline awareness would add to costs of producing and distributing the written information Supermarkets may receive more requests to distribute information than they can handle Supermarket customers may not attend to checkout literature if its volume were to increase Other folate-related health promotion that took place before the 3-

	since this is a study that aimed only to increase awareness Three years later overall awareness was higher, but other folate-related health promotion had occurred in the meantime	intervention such as this may not be effective for women 15-24y At 3 years awareness also varied significantly by education (tertiary educated women more likely to be aware)				year follow-up included advertising by breakfast cereal manufacturers

5.2. Key question 2: What interventions are effective in increasing uptake of folic acid supplements in non-pregnant women of child bearing age who are planning a pregnancy or might become pregnant?

Ray (2004) carried out a SR (2+) to examine rates of folic acid supplement use, both pre-conceptionally and peri-conceptionally. They also aimed to identify characteristics associated with low rates of use, and to assess whether folic acid awareness campaigns were associated with higher folic acid use. Fifty-two reports were included in this SR – the majority from developed countries, though a large Chinese survey of 247831 women was also included. Thirty-four studies surveyed *pre-conceptional* folic acid use; the lowest rate was observed in southern Israel in 1999 (0.9%) and the highest rate was observed in Vancouver, Canada in 1999 (49%). Forty nine studies surveyed *peri-conceptional* folic acid use with the lowest rate in eastern Sicily, Italy in 1997/8 (0.5%) and the highest rate in the Netherlands in 1998 (52%). Factors associated with low peri-conceptional folic acid use (30 studies, $p<0.05$) included a lower level of formal education, immigrant status, young maternal age, lack of a partner, and unplanned pregnancy (often associated with >50% reduction in use).

Four studies included in this SR evaluated changes in peri-conceptional folic acid use following mass media health campaigns (none of these studies were given quality scores by the authors of the SR). The HEA campaign conducted in the UK in 1996 was designed to increase public and professionals' awareness of and access to folic acid fortified foods and supplements using TV and magazines. Sillender (2000) observed an increase in folic acid use after the campaign: RR 1.8, 95% CI 1.3-2.4. The Dutch 'Folic Acid Campaign' in 1995 was a media campaign aimed at the public and professionals - for women wishing to conceive 'planners' and 'future planners' and their heath care professionals. It also involved personal letters to the health professionals. The first evaluation of the campaign was by Van der Pal-de-Bruin (2000) giving a RR for folic acid use of 4.4, 95% CI 3.5-5.6. The campaign was further evaluated three years later by De Walle (2002) who paid special attention to women of lower socio-economic status. They observed an increased rate of tablet use: RR of 7.2, 95% CI 4.4-11.6. The third campaign was in South Australia: the 'Folate Before Pregnancy' campaign conducted in 1995. This campaign included telephone messages, leaflets, newspaper messages and occasional TV announcements. This campaign resulted in increased folic acid use: RR 1.7, 95% CI 1.3-2.3 (Chan, 2001). Folic acid use therefore significantly increased by a factor of

between 1.7 to 7.2 but in no study was the post campaign rate of folic acid use >50%. The Dutch campaign was apparently the most successful.

A RCT by Robbins et al (2005) (1+) evaluated the impact of a physician intervention during routine gynaecological visits on folic acid supplementation. The participants were women aged between 18 and 45 years from a range of socio-economic backgrounds living in the US (n=322). The intervention involved 30 to 60 seconds of scripted counselling from the gynaecologist on the benefits of folic acid supplements and the need for all women to take a folic acid supplement. The intervention group also received 30 folic acid tablets at the visit, written information about the benefits of folic acid supplements, and a booster phone call from a research nurse one to two weeks later. The control group received 30 to 60 seconds of scripted physician counselling on one of three preventive behaviours (breast self-examination, seat belt use or sunscreen use), a coupon for 30 free folic acid tablets with a prepaid envelope to claim them, plus the same written information about folic acid supplements as the intervention group. Physicians were not prohibited from including folic acid in their advice to women in the control group. Self-reported daily folic acid use did not differ significantly between the groups before and two months after the intervention (n=279). Use of folic acid supplements at least weekly (but less than daily) increased from 38% before the intervention to 64% after in the intervention group compared with 43% before and 51% after in the control group (p=0.008). Sub-group analysis demonstrated that black and lower income women were most influenced by the intervention.

A UK prospective cohort survey (3+) provides some useful additional information. It examined socio-demographic variables associated with the use of supplements containing folic acid prior to conception and in the first trimester of pregnancy (Mathews 1998). The survey found that of 963 women from Portsmouth, 32% of pregant women reported using supplements containing folic acid prior to conception, and 38% took folic acid after becoming pregnant. The use of folic acid supplements before pregnancy and in the first trimester was positively related to maternal age, education, social class and living with a partner (p<0.001).

Strength and applicability of evidence

One SR (Ray 2004) provides level 2+ evidence that mass media campaigns conducted in developed countries significantly increased peri-conceptional folic acid use, but in no study was the post campaign rate of folic acid use >50%. Based on 30 studies, this SR also reported that the risk factors for low peri-conception folic acid use include low levels of formal education, young maternal age, lack of a partner, immigrant status and unplanned pregnancy.

One RCT (Robbins 2005) provides level 1+ evidence that brief counselling from a physician about the benefits of folic acid along with the provision of free folic acid supplements effectively increased weekly, but not daily, folic acid supplement use in a sample of US women.

Reference	How does the structure and content of the intervention influence effectiveness?	Does effectiveness vary by gender, age, ethnicity, religious practices or social/ professional group of those receiving or delivering the intervention ?	Does effectiveness vary with site/ setting or intensity/ duration of the intervention ?	What are the views of those receiving and delivering the intervention ?	Is there evidence of unintended or harmful effects?	Are there barriers to replication of effective interventions?
Robbins 2005	It is not clear how much of the effectiveness of the intervention was due to the telephone reminder at 2 weeks	Subgroup analyses showed greater folic acid use among black women (p=0.003), those with household income <$30,000 (p=0.007), those not planning pregnancy (p<0.001) and those aware of benefits of folic acid (p=0.005)	Not reported	Not reported	No	Barriers to counselling and written information not apparent The telephone reminder might not transfer so well to standard UK care

5.3. Key question 3: What interventions are effective in increasing dietary folate in women of child bearing age who are planning a pregnancy or might become pregnant?

No systematic reviews were identified in our literature search that addressed this question. One study was found which was of some relevance this was an RCT (1-) that examined two dietary interventions in overweight women of childbearing age (n=67), with the aim of assessing their impact on weight loss and folate status (Ortega 2006). The participants in this study were largely university students living in Madrid, Spain. Both groups restricted energy-rich foods while one increased consumption of vegetables, and the other increased consumption of breakfast cereals fortified with folic acid. The authors reported significantly greater weight loss ($p<0.05$) and serum folate ($p<0.001$) after six weeks in the women eating more cereals.

A UK survey (3+) provides some additional contextual information. It examined folate intake as well as folic acid supplementation in a sample of women at <20 weeks gestation (n=154) (Elkin 2000). Those women who had previously experienced recurrent miscarriage or second trimester pregnancy loss had better knowledge and compliance with taking folic acid supplements than those who had had uncomplicated pregnancies, whether they were recent or not. Fifty one percent of women with pregnancy complications took folic acid supplements for the recommended time period versus 26% of those with no complications. Health professionals were the main information source and more women were aware of the need for pre-conceptional folic acid supplements than post-conceptional folic acid supplements. Dietary knowledge of folate-rich foods was poor and only one woman had increased her intake of folate-rich foods and then only post-conceptionally. There was no apparent correlation between recent (within 24 h) dietary folate intake and serum folate in women, whether or not they were taking or had taken folic acid supplements.

Strength and applicability of evidence

One RCT (Ortega 2006) provides level 1- evidence that an energy restricted diet and increased consumption of breakfast cereals (fortified with folic acid) significantly increases serum folate in women in comparison to those with an energy restricted diet and increased consumption of vegetables.

This study may be applicable to women in the UK, although recommendations based on this study may be limited.

Reference	How does the structure and content of the intervention influence effectiveness?	Does effectiveness vary by gender, age, ethnicity, religious practices or social/ professional group of those receiving or delivering the intervention?	Does effectiveness vary with site/ setting or intensity/ duration of the intervention?	What are the views of those receiving and delivering the intervention?	Is there evidence of unintended or harmful effects?	Are there barriers to replication of effective interventions?
Ortega 2006	Paper reports that 11% of women in the vegetable group, and 10% of women in the cereal group declared taking folic acid on a sporadic basis. Similarly, 42% of	Not reported	Results significant at 2 weeks and 6 weeks after the intervention	Not reported	No	Fortified breakfast cereals are available in the UK – but may not be appropriately recommended to women trying to lose

Reference	How does the structure and content of the intervention influence effectiveness?	Does effectiveness vary by gender, age, ethnicity, religious practices or social/ professional group of those receiving or delivering the intervention ?	Does effectiveness vary with site/ setting or intensity/ duration of the intervention ?	What are the views of those receiving and delivering the intervention ?	Is there evidence of unintended or harmful effects?	Are there barriers to replication of effective interventions?
	women in the control group declared taking foods fortified with folic acid					weight

5.4. Key question 4: What interventions are effective in increasing health professionals' knowledge and awareness of the recommendations for folate and folic acid in women of child bearing age who are planning a pregnancy or might become pregnant?

No systematic reviews or randomised control trials were identified in our literature search that addressed this question. A before-and-after study (2+) evaluated the HEA folic acid campaign on professionals' knowledge of folic acid for women planning a pregnancy/pregnant women (HEA, 1998). The campaign included a combination of publications, advertising, media work and professional seminars to dieticians, family planning doctors and nurses, GPs, health promotion specialists, health visitors, midwives, nutritionists, obstetricians, pharmacists, practice nurses, public health professionals, school-based professionals and others in contact with young people. In 1996, only 55% of health professionals surveyed stated that they spontaneously mentioned folic acid when giving advice to women planning a pregnancy, compared to 71% in 1997. In 1996, only 41% health professionals surveyed knew the correct dosage of folic acid needed in women planning a pregnancy. This figure remained relatively low in the 1997 survey (45%). In both surveys, 73% of the professionals knew that folic acid was to be taken before conception and in the first twelve weeks.

Some additional information is provided by a UK qualitative survey (3+) that evaluated pharmacists and medicine counter assistants experience of using promotional materials produced by the HEA and National Pharmaceutical Association (Anderson 2002). These materials promoted the use of folic acid supplements (400 µg/day) by women prior to conception and in the first 12 weeks of pregnancy. Pharmacists and medicine counter assistants attended a training course and reported their experience of using the materials in interviews (n=28). The staff felt they would only raise the issue with regular customers they knew well or if asked.

The participants thought that raising awareness among unknown customers was probably limited to leaflets, displays and posters. The study was carried out in West London in a community with a large number of South Asian women. Minority ethnic staff felt they had an important role in communicating with customers from their own ethnic group, provided they spoke the same language.

Strength and applicability of evidence

One large before-and-after survey (HEA 1998) provides level 2+ evidence that the HEA folic acid campaign increased the percentage of health professional who gave folic acid advice to women planning a pregnancy. The survey also found that many health professionals working in the UK in 1997 had gaps in their knowledge about the appropriate dosage and timing of folic acid for women.

5.5. Key question 5: What interventions (other than those about folate or folic acid) improve nutritional status of women of child bearing age who are planning a pregnancy or might become pregnant?

One systematic review (Van Teijlingen, 1998), one randomised control trial (Doyle et al., 2001) and one before-and-after study (Doyle et al., 1999) were identified in our literature search that addressed this question. The aim of the systematic review was to evaluate the effectiveness of interventions to promote healthy eating in women of childbearing age, as well as pregnant women. As a systematic review, it was methodologically well conducted (2++). However, out of nine included studies, five concerned women of childbearing age, and of these, only one study specifically aimed to improve dietary knowledge in young women (Fine et al., 1994). The objectives of the other studies were diverse – including reducing the risk of specific diseases (Cox et al., 1995; Brown et al., 1996), improving child health (Johnson et al., 1993), or investigating the dietary behavioural correlates of strength training (Tucker et al., 1996). While three of the studies specifically targeted women of childbearing age (although not necessarily with the aim of improving reproductive health), two others were aimed at an adult female population and included post-menopausal women (Brown et al., 1996; Tucker et al., 1996).

The authors of the systematic review note the diversity and methodological limitations of the studies included in their review, and are cautious with their conclusions – which state that women of childbearing age can improve their knowledge and dietary intake, particularly a reduction in fat intake (% energy). However, for the purposes of this rapid review, one study included in the systematic review by Van Teijlingen et al.,1998 will be briefly considered in more detail (Fine et al., 1994) as the intervention and population sample are more directly relevant to the research question.

This UK-based RCT was conducted in young women from lower-income households (Fine et al., 1994). It aimed to assess the effectiveness of basic nutrition education delivered using printed material (with or without a one-off video) on nutritional knowledge. After one week, knowledge scores (not defined) were significantly higher in women receiving the intervention compared to women who received no intervention ($p<0.05$). The quality of this study was assessed by Van Teijlingen et al., 1998, and is reported to have several methodological limitations; it is also limited in its duration, thus having an unknown long-term impact.

Doyle et al (2001) (1-) examined whether micronutrient supplementation during the inter-pregnancy interval improved the nutritional status of women with poor diets who

had had a low-birthweight baby and planned a further pregnancy. This was part of a larger study of women living in a deprived inner city area of London who were mothers of low-birthweight babies and intended to have further pregnancies. Thirty-four English-speaking mothers found to have a diet meeting fewer than four of sixteen dietary reference values were randomised to daily multivitamin-mineral and docasahexaenoic acid (single cell oil) supplements from three to nine months postpartum with advice (intervention group n=17) or advice only (control group n=17). Analysis included only those who completed the study. Six mothers in the intervention group (35%) did not like the supplements; results from these and from one mother who dropped out of the control group are not reported. There were inter-group differences among those who completed the study. The control group included all of the teenagers as well as more older and white women and more mothers of small and premature babies. For those who completed the study, at nine months postpartum, mean serum folate was 12.5 nmol/l in the intervention group and 5.57 nmol/l in the control group ($p<0.001$), mean erythrocyte folate was 346 nmol/l and 255 nmol/l ($p=0.009$) and mean serum ferritin 36.0 μg/l and 25.4 μg/l respectively ($p=0.034$). Differences in mean haemoglobin (12.6 g/dl vs. 13.1 g/dl) were not statistically significant.

A before-and-after study (2-) evaluated the effectiveness of nutritional counselling of mothers in the inner city of London who had previously had a baby weighing ≤2.5 kg and who intended having another baby in the future (n=640) (Doyle 1999). The intervention involved counselling sessions with a dietician, monthly group events, and two newsletters that aimed to maintain the participants awareness of the project. After six months, there were significant increases in the mean intakes of protein, niacin and vitamin B6 ($p<0.04$), but no increases in a number of other daily intakes. Mothers' views on nutrition were also assessed – a relatively high number (21-34%) had a low level of knowledge or interest in nutrition and the impact on their baby's health, and most (83%) based their family meals on their partner's and family's preferences. The authors of this feasibility study concluded that counselling alone was not effective in improving nutritional intake in this sample of women.

Strength and applicability of evidence

One SR (2++) (Van Teijlingen 1998) which aimed to evaluate the effectiveness of interventions to promote healthy eating in women of childbearing age found no high quality studies that show that nutritional interventions may effectively promote healthy eating in women of childbearing age.

One RCT (Doyle 2001) provides level 1- evidence that multivitamin-mineral and single cell oil containing docosahexaenoic acid supplements (that included iron and folate) were effective in raising blood levels of iron and folate in postpartum women who were found to have a diet meeting fewer than four of sixteen dietary reference values.
This study is directly applicable to UK mothers with poor diets.

Reference	How does the structure and content of the intervention influence effectiveness?	Does effectiveness vary by gender, age, ethnicity, religious practices or social/ professional group of those receiving or delivering the intervention?	Does effectiveness vary with site/ setting or intensity/ duration of the intervention?	What are the views of those receiving and delivering the intervention?	Is there evidence of unintended or harmful effects?	Are there barriers to replication of effective interventions?
Doyle 2001	The intervention was free supplements to be taken daily. Compliance was checked 3-weekly, and those who took the supplements at all (11/17) took them 5 or more times per week. It is not clear how much this level of compliance depended on the 3-weekly checks	Younger mothers tended to have an inadequate diet	Not applicable	6/17 allocated to supplements dropped out because they did not like the supplements	No	Authors recommend routine folate and iron supplementation at least to women with a small baby planning further pregnancies Cost barriers to this not apparent

6. Discussion

This rapid review examined the effectiveness of public health interventions provided to women of childbearing age during and around pre-conception and or peri-conception to improve nutrition/health outcomes. The review particularly focussed on folic acid/folate use and awareness because this is known to reduce the incidence of babies born with neural tube defects. The search strategy undertaken was comprehensive and stakeholders and PDG members were also able to suggest additional relevant studies but very few studies were found and some of the studies were of relatively poor quality.

It is acknowledged that undertaking RCTs to evaluate interventions to increase public awareness is difficult and that this method may not always be appropriate given that information could easily cross between intervention and control areas. The most consistent positive results for increasing folate awareness and/or the uptake of folic acid supplements are derived from survey studies of mass media interventions – including the 'The Health Authority Folic Acid Campaign' conducted in the UK between 1995-1998. It is noted however, that in no study, was the post campaign rate of folic acid use greater than 50%. This indicates that media campaigns alone are unlikely to be sufficient if the aim is to maximise the proportion of women that reach the recommended levels of folate intake.

No studies of sufficient quality were found that evaluated interventions to increase folate consumption in women that are planning a pregnancy or might become pregnant. The lack of studies may reflect difficulties in recruiting an appropriate study population and measuring folate consumption.

For practical reasons, surveys have relied on self-reported intake or proxy measures such as prescription rates or changes in sales of folic acid supplements. Evidence from one UK study (Elkin 2000) indicates that it may be difficult to achieve sufficient increases in dietary folate. Perhaps focussing on increased uptake of supplements and/or fortification may be more effective than promoting dietary folate alone. The COMA review of the Welfare Food Scheme (DH 2002 cited in the draft SACN Report 2005) considered the merits of providing free peri-conceptional folic acid supplements to beneficiary population groups. The review highlights that the uptake of supplements by groups eligible under the Scheme was poor (SACN 2005 p 15). Although studies on fortification of food did not fall within the remit of this review, it was notable that many authors of the studies in this review concluded that this could be the best approach, especially considering the rate of unplanned pregnancies.

Very few intervention studies have evaluated ways to improve the nutrition of women of childbearing age. This is shown both by this search of the literature and the results of a well conducted systematic review (Van Teijlingen, 1998). This lack of high quality evidence almost certainly reflects the difficulties in undertaking such studies. Recruiting and retaining a study population of women that might benefit from a nutrition intervention is likely to be very difficult. The lack of evidence and complete absence of any high quality randomised control trials meant that no conclusions about general nutrition interventions to improve health and pregnancy outcomes in women that might become pregnant could be made.

7. Conclusions

Pre-conception care has the potential to improve pregnancy outcomes for both mother and foetus but there was a lack of high quality studies that evaluated the link between the general nutritional status of women of childbearing age and nutrition/health outcomes.

Mass media campaigns have been successful in increasing folate awareness and/or the uptake of folic acid supplements. Effective campaigns included leaflets, newspaper and television announcements, telephone messages and personal letters to health professionals. The evidence although sparse suggests that interventions aimed at increasing dietary intake of folate-rich foods are unlikely to be effective.

Appendix A – Included Studies

Systematic reviews

Ray JG, Singh G, Burrows RF (2004) Evidence for suboptimal use of periconceptional folic acid supplements globally. *BJOG: an International Journal of Obstetrics and Gynaecology* 111: 399-408.

van Teijlingen E, Wilson B, Barry N et al. (1998) Effectiveness of interventions to promote healthy eating in pregnant women and women of childbearing age: a review. London: Health Education Authority.

Randomised controlled trials

Doyle W, Srivastava A, Crawford MA et al. (2001) Inter-pregnancy folate and iron status of women in an inner-city population. *British Journal of Nutrition* 86(1): 81-7.

Ortega RM, Lopez-Sobaler AM, Andres P et al (2006) Changes in folate status in overweight/obese women following two different weight control programmes based on an increased consumption of vegetables or fortified breakfast cereals. *British Journal of Nutrition* 96(4):712-8.

Robbins JM, Cleves MA, Collins HB 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.

Watson M, Watson L, Bell R et al. (2001) The increasing knowledge of the role of periconceptional folate in Victorian women of child-bearing age: follow-up of a randomised community intervention trial. *Australian & New Zealand Journal of Public Health* 25(5): 389-95.

Watson MJ, Watson LF, Bell RJ 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): 255-65.

UK studies

Anderson C and Rajyaguru R (2002) The role of community pharmacists and medicines counter assistants in health promotion: Reflections from a folic acid campaign. *International Journal of Pharmacy Practice* 10 (1): 17-22.

Doyle W, Crawford MA, Srivastava A et al. (1999) Interpregnancy nutrition intervention with mothers of low-birthweight babies living in an inner city area: a feasibility study. *Journal of Human Nutrition and Dietetics* 12 (6): 517-27.

Elkin AC and Higham J (2000) Folic acid supplements are more effective than increased dietary folate intake in elevating serum folate levels. *BJOG: An International Journal of Obstetrics & Gynaecology* 107 (2): 285-9.

Health Education Authority (1998) Changing Preconceptions: The HEA Folic Acid Campaign 1995-1998.

Mathews F, Yudkin P and Neil A (1998) Folates in the periconceptional period: are women getting enough? *British Journal of Obstetrics & Gynaecology* 105 (9): 954-9.

Pearson S, Dimond H, Ford F et al. (1996) A survey of pre-pregnancy nutritional knowledge in family planning clinics. *The British Journal of Family Planning* 22: 92-4.

Studies included in Systematic Reviews included in this Rapid Review

Edwin van Teijlingen (1998):

Brown 1996
Brown WJ, Lee C, Oyomopito R (1996) Effectiveness of a bilingual heart health program for Greek-Australian women. Health Promotion International 11:117-25.

Cox 1995
Cox RH, Parker GG, Watson AC et al. (1995) Dietary cancer risk of low-income women and change with intervention. American Dietetic Association Journal 95: 1031-4.

Fine 1994
Fine GA, Conning DM, Firmin C et al. (1994) Nutrition education of young women. British Journal of Nutrition 71: 789-98.

Johnson 1993
Johnson Z, Howell F, Molloy B (1993) Community mothers' programme: randomised controlled trial of non-professional intervention in parenting. British Medical Journal 306: 1449-52.

Tucker 1996
Tucker LA, Harris K, Martin JR (1996) Participation in a strength training program leads to improved dietary intake in adult women. American Dietetic Association Journal 96: 388-90.

Ray (2004):

Chan 2001
Chan A, Pickering J, Haan E et al. (2001) Folate before pregnancy: the impact on women and health professionals of a population-based health promotion campaign in South Australia. Medical Journal of Australia 174: 631-636.

De Walle 2002
De Walle HE, Cornel MC, de Jong-van den Berg LT (2002) Three years after the Dutch folic acid campaign: growing socioeconomic differences. Preventive Medicine 35: 65-69.

De Walle HE, de Jong-van den Berg LT (2002) Insufficient folic acid intake in the Netherlands: what about the future? Teratology 66: 40-43.

Sillender 2000

Sillender M, Pring DW (2000) How effective was the Health Education Authority's folic acid campaign? Journal of Obstetrics and Gynaecology 20: 271-276.

Van der Pal-de-Bruin 1995
Van der Pal-de Bruin KM, de Walle HE, Jeeninga W et al. (2000) The Dutch 'Folic Acid Campaign' – have the goals been achieved? Paediatric and Perinatal Epidemiology 14: 111-117.

APPENDIX B – Excluded Studies

Paper – Systematic Reviews	*Reason for Exclusion*
Agency for Healthcare Research and Quality (2006) Screening for iron deficiency anemia in childhood and pregnancy: Update of the 1996 U.S. Preventive Task Force Review. *Rockville, MD: Agency for Healthcare Research and Quality (AHRQ):* http://www.ahrq.gov/clinic/uspstf/upsiron.htm	Screening, effectiveness of supplements for people with iron deficiency anaemia
Andrews JO, Felton G, Wewers ME et al. (2004) Use of community health workers in research with ethnic minority women. *Journal of Nursing Scholarship* 36(4): 358-65.	No relevant review outcomes
Balas EA, Weingarten S, Garb CT et al. (2000) Improving preventive care by prompting physicians. *Archives of Internal Medicine* 160(3): 301-8.	No relevant review outcomes
Blondel B, Breart G. (1995) Home visits during pregnancy: consequences on pregnancy outcome, use of health services, and women's situations. *Seminars in Perinatology* 19(4): 263-71.	No defined nutrition intervention
Bradley KA, Boyd-Wickizer J, Powell SH et al. (1998) Alcohol screening questionnaires in women: a critical review. *Journal of the American Medical Association* 280(2): 166-71.	Screening only, no relevant review outcomes
Brunton G, Thomas H (2001) The effectiveness of public health strategies to reduce or prevent the incidence of low birth weight in infants born to adolescents: a systematic review. *Hamilton, ON, Canada: City of Hamilton Social and Public Health Services Department. Effective Public Health Practice Project.*	Intervention not nutrition, intervention in later pregnancy
Ciliska D, Mastrilli P, Ploeg J et al. (1999) The effectiveness of home visiting as a delivery strategy for public health nursing interventions to clients in prenatal and postnatal period: a systematic review. *Dundas, ON, Canada: Ontario Ministry of Health Region of Hamilton- Wentworth Social and Public Health Services Division. Effective Public Health Practice Project*.	No relevant review outcomes
D'Onofrio G, Degutis LC (2002) Preventive care in the emergency department. Screening and brief intervention for alcohol problems in the emergency department: a systematic review. *Academic Emergency Medicine* 9(6): 627-38.	Participants - general population in hospital A & E Departments
Fiscella K (1995) Does prenatal care improve birth outcomes: a critical review. *Obstetrics and Gynecology* 85(3): 468-79.	Intervention with no nutritional components
Fugh-Berman A, Kronenberg F (2003) Complementary and alternative medicine (CAM) in reproductive-age women: a review of randomized controlled trials. *Reproductive Toxicology* 17(2): 137-52.	No relevant outcomes – symptom relief only
Gepkens A, Gunning-Schepers LJ (1996) Interventions to reduce socioeconomic health differences: a review of the international literature. *European Journal of Public Health* 6(3): 218-26.	No relevant review outcomes
Korenbrot CC, Steinberg A, Bender C et al. (2002)	Outcome – incidence

Preconception Care: a systematic review. *Maternal and Child Health Journal* 6(2): 75-88.	of NTDs only
Kramer MS (1996) Nutritional advice in pregnancy. *The Cochrane Database of Systematic Reviews*: Reviews 1996 Issue 4 DOI: 101002/14651858CD000149.	Review withdrawn
Lister-Sharp D, Chapman S, Stewart-Brown S et al. (1999) Health promoting schools and health promotion in schools: two systematic reviews. *Health Technology Assessment* 3(22): 1-207.	No relevant review outcomes
Lumley J, Watson L, Watson M et al. (2001) Peri-conceptional supplementation with folate and/or multivitamins for preventing neural tube defects. *The Cochrane Database of Systematic Reviews: Reviews 2001* Issue 3 UK DOI: 01002/14651858CD001056.	Included in original rapid review
Mahomed K (1997) Folate supplementation in pregnancy. *The Cochrane Database of Systematic Reviews:* Reviews 1997 Issue 3 DOI: 101002/14651858CD000183.	The role of peri-conceptional folic acid supplementation was specifically not addressed (supplementation throughout pregnancy only)
Mahomed K, Gülmezoglu AM (1997) Maternal iodine supplements in areas of deficiency. *The Cochrane Database of Systematic Reviews:* Reviews 1997 Issue 4 DOI: 101002/14651858CD000135.	Not preconception, not periconception
Mozaffarian D, Rimm E B (2006) Fish Intake, Contaminants, and Human Health: evaluating the risks and the benefits. *Journal of the American Medical Association* 296(15): 1885-1899.	Not a SR of intervention studies
Pelletier KR (2001) A review and analysis of the clinical- and cost-effectiveness studies of comprehensive health promotion and disease management programs in the worksite: 1998-2000 update. *American Journal of Health Promotion* 16(2): 107-16.	No relevant review outcomes
Rumbold A, Middleton P, Crowther CA (2005) Vitamin supplementation for preventing miscarriage. The *Cochrane Database of Systematic Reviews: Reviews* Issue 2 UK DOI: 101002/14651858CD004073pub2.	Included in original rapid review
Tedstone A, Dunce N, Aviles M et al. (1998) Effectiveness of interventions to promote healthy feeding in infants under one year of age. *London: Health Education Authority. Health Promotion Effectiveness Reviews*; 9.	Participants are infants
Wade K, Cava M, Douglas C et al. (1999) A systematic review of the effectiveness of peer/paraprofessional 1:1 interventions targeted towards mothers (parents) of 0-6 year old children in promoting positive maternal (parental) and/or child health/developmental outcomes*. Dundas, ON, Canada: Ontario Ministry of Health Region of Hamilton-Wentworth Social and Public Health Services Division. Effective Public Health Practice Project*.	No relevant review outcomes

Paper – Randomised Controlled Trial	*Reason for*

	Exclusion
Ahn E, Kapur B, Koren G (2005) Study on circadian variation in folate pharmacokinetics. *Canadian Journal of Clinical Pharmacology/Journal Canadien de Pharmacologie Clinique* 12(1): e4-9.	Timing of folate supplements
Allen LH (2005) Multiple micronutrients in pregnancy and lactation: An overview. *American Journal of Clinical Nutrition* 81(5): 1206S-12S.	Not an SR or an RCT, narrative review – data from Nepal
Anderson AS, Campbell DM, Shepherd R (1995) The influence of dietary advice on nutrient intake during pregnancy. *British Journal of Nutrition* 73(2): 163-77.	All participants were in third trimester
Bailey LB, Berry RJ (2005) Folic acid supplementation and the occurrence of congenital heart defects, orofacial clefts, multiple births, and miscarriage. *American Journal Of Clinical Nutrition* 81(5): 1213S-7S.	Not an SR or an RCT, narrative review
Bering S, Suchdev S, Sjøltov L, Berggren A, Tetens I, Bukhave K (2006) A lactic acid-fermented oat gruel increases non haem iron absorption from a phytate-rich meal in healthy women of childbearing age. *British Journal of Nutrition* 96:80-85.	Not a public health intervention
Bower C, Stanley FJ (1992) Periconceptional vitamin supplementation and neural tube defects; evidence from a case-control study in Western Australia and a review of recent publications.[erratum appears in *Journal of Epidemiology & Community Health* (1992) 46(3): 316]. *Journal of Epidemiology & Community Health*. 46(2): 157-61.	Not an SR or an RCT, narrative review, outcome – incidence of NTDs only
Bower C, Stanley FJ (2004) Case for mandatory fortification of food with folate in Australia, for the prevention of neural tube defects. *Birth Defects Research* 70(11): 842-3.	Not a study – argue for fortification
Briley C, Flanagan NL, Lewis N (2002) In-home prenatal nutrition intervention increased dietary iron intakes and reduced low birthweight in low-income African-American women. *Journal of the American Dietetic Association* 102(7): 984-7.	All participants were in third trimester
Bussell G and Marlow N (2000) The dietary beliefs and attitudes of women who have had a low-birthweight baby: a retrospective preconception study. *Journal of Human Nutrition and Dietetics* 13:29-39.	No intervention
Chan A, Pickering J, Haan E et al. (2001) Folate before pregnancy: the impact on women and health professionals of a population-based health promotion campaign in South Australia.[see comment]. *Medical Journal of Australia* 174(12): 631-6.	RCT already included in SR
Chang G, Wilkins-Haug L, Berman S et al. (1999) Brief intervention for alcohol use in pregnancy: a randomized trial. *Addiction* 94(10): 1499-508.	Included in original rapid review
Chang G, McNamara TK, Orav EJ et al. (2005) Brief intervention for prenatal alcohol use: a randomized trial. *Obstetrics & Gynecology* 105(5 Pt 1): 991-8.	Included in original rapid review
Czeizel AE, Dudas I, Fritz G et al. (1992). The effect of periconceptional multivitamin-mineral supplementation on vertigo, nausea and vomiting in the first trimester of pregnancy. *Archives of Gynecology & Obstetrics* 251(4): 181-	RCT already included in SR

5.	
Dobo M, Czeizel AE (1998) Long-term somatic and mental development of children after periconceptional multivitamin supplementation. *European Journal Of Pediatrics* 157(9): 719-23.	RCT already included in SR
Galletly C, Clark A, Tomlinson L et al. (1996) Improved pregnancy rates for obese, infertile women following a group treatment program: An open pilot study. *General Hospital Psychiatry* 18(3): 192-5.	Infertile women
Grant TM, Ernst CC, Streissguth A et al. (2005) Preventing alcohol and drug exposed births in Washington state: intervention findings from three parent-child assistance program sites. *The American Journal Of Drug And Alcohol Abuse* 31(3): 471-90.	Participants were a mixture of pregnant and non-pregnant women, with an established drug/alcohol abuse program
Howell SR, Barnett AG and Underwood MR (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): 300-303.	No intervention
Jack BW, Culpepper L, Babcock J, Kogan MD, Weismiller D (1998) Addressing preconception risks identified at the time of a negative pregnancy test: a randomized trial. *The Journal of Family Practice* 47(1): 33-38.	No nutrition intervention
Jensen TK, Henriksen TB, Hjollund NH et al. (1998) Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. *Reproductive Toxicology* 12(3): 289-95.	No intervention
de Jong-Potjer LC, de Bock GH, Zaadstra BM, de Jong ORW, Verloove-Vanhorick SP, Springer MP (2003) Women's interest in GP-initiated pre-conception counselling in The Netherlands. *Family Practice* 20(2):142-6.	No nutrition intervention
Kinzie MB, Schorling JB, Siegel M (1993) Prenatal alcohol education for low-income women with interactive multimedia. *Patient Education and Counseling* 21(1-2): 51-60.	Participants mainly third trimester
Kulier R, De Onis M, Gülmezoglu AM et al. (1998) Nutritional interventions for the prevention of maternal morbidity. *International Journal of Gynecology & Obstetrics* 63(3): 231-46.	Included in original rapid review
Little RE and MacGillivray I (1995). Abstinence from alcohol before pregnancy and reproductive outcome. *Paediatric and Perinatal Epidemiology* 9 (1): 105-8.	Included in original rapid review
Lunet N, Rodrigues T, Barros H (2003) Pregnancy planning and vitamin/mineral use during pregnancy: Results from a study in Portugal. *Preventive Medicine: An International Journal Devoted to Practice and Theory* 37(1): 71.	No intervention
Manwell LB, Fleming MF, Mundt MP et al. (2000) Treatment of problem alcohol use in women of childbearing age: results of a brief intervention trial. *Alcoholism: Clinical & Experimental Research* 24(10): 1517-24.	Participants had an established drink problem, no pregnancy outcomes
Merialdi M, Carroli G, Villar J et al. (2003) Nutritional interventions during pregnancy for the prevention or treatment of impaired fetal growth: An overview of	Pregnant women (not pre- or peri-conception), infant

randomized controlled trials. *Journal Of Nutrition* 133(5 SUPPL. 1): 1626S-31S.	outcomes only
Metneki J, Dudas I, Czeizel AE (1996) Higher rate of multiple births after periconceptual multivitamin supplementation. *Orvosi Hetilap* 137(43): 2401-5.	Not English – included in Lumley and Rumbold SR's
O'Brien MM, Kiely M, Harrington KE et al. (2001) The North/South Ireland Food Consumption Survey: vitamin intakes in 18-64-year-old adults. *Public Health Nutrition* 4(5A): 1069-79.	No intervention
Quinn GP, Hauser K, Bell-Ellison BA, Rodriguez NY, Frías JL (2006) Promoting pre-conceptional use of folic acid to Hispanic women: a social marketing approach. *Maternal and Child Health Journal* 10(5): 403-412.	Not a RCT
Reynolds KD, Coombs DW, Lowe JB et al. (1995) Evaluation of a self-help program to reduce alcohol consumption among pregnant women. *The International Journal of the Addictions* 30(4): 427-43.	Included in original rapid review
Rolschau J, Kristoffersen K, Ulrich M et al. (1999) The influence of folic acid supplement on the outcome of pregnancies in the county of Funen in Denmark. *Part I. European Journal of Obstetrics, Gynecology, & Reproductive Biology*. 87(2): 105-10.	Study compares two doses of folic acid, neither of which are currently recommended in the UK
Rosenberg KD, Gelow JM, Sandoval AP (2003) Pregnancy intendedness and the use of periconceptional folic acid. *Pediatrics* 111(5 Part 2): 1142-5.	No intervention
Slawson D (2000) Can fish oil supplementation in pregnant women reduce the risk of recurrent preterm delivery? *Evidence-Based Practice* 3(8) Part 7: insert 2p.	Abstract only
Velie EM, Block G, Shaw GM et al. (1999) Maternal supplemental and dietary zinc intake and the occurrence of neural tube defects in California. *American Journal Of Epidemiology* 150(6): 605-16.	No intervention
Wald NJ, Law MR, Morris JK et al. (2001) Quantifying the effect of folic acid.[see comment][erratum appears in *Lancet* 2002 Feb 16;359(9306): 630]. *Lancet* 358(9298): 2069-73.	Not an SR or an RCT, outcome on dosage level only
Williamson CS (2006) Nutrition in pregnancy. *Nutrition Bulletin* 31(1): 28-59.	No intervention

Studies suggested by stakeholder or Programme Development Group committee member	**Reason for exclusion**
Bussell G, Marlow N. The dietary beliefs and attitudes of women who have had a low birthweight baby: a retrospective preconception study. Unpublished paper (2006)	Not an intervention study
Seddon T (for the Health Education Authority) Folic Acid Research Report, December 1999	Included as part of the folic acid campaign evaluation
Wigda AC, Lewis NM (1999) Defined, in-home, prenatal nutrition intervention for low-income women. Journal of the	Not about

American Dietetic Association Vol 99 No 9 pp 1058-62	preconception period
Williams P et al. (2001) Impact evaluation of a folate education campaign with and without the use of a health claim. Australian and New Zealand Journal of Public Health Vol 25 No 5 pp 396-404	Not an RCT
Reid M, Adamson H. Opportunities for and barriers to good nutritional health in women of childbearing age, pregnant women, infants under 1 and children aged 1 to 5. Health Education Authority, 1997	Not an intervention study
Villamore E, Cnattingius S (2006) Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. Lancet Vol 368 pp 1164-70	Not an intervention study

APPENDIX C – Search Strategy

Searches for NICE Rapid Review "The effectiveness of public health interventions to promote nutrition of pre-conceptional women".

Stage one of the literature search was to identify systematic reviews by searching the Cochrane Database of Systematic Reviews, DARE, the Health Technology Assessment database and the Ongoing Reviews Register. Details of the search strategies used are listed below.

In addition, a number of web sites were scanned/searched to identify possibly relevant reviews. These were:
SIGN Guidelines http://www.sign.ac.uk
National Guideline Clearinghouse http://www.ahcpr.gov/clinic/assess.htm
National Coordinating Centre for Health Technology Assessment
http://www.hta.nhsweb.nhs.uk
NICE web pages (published appraisals) http://www.nice.org.uk/nice-web/
HSTAT http://text.nlm.nih.gov/
The Department of Health Research Findings electronic Register
TRIP http://www.tripdatabase.com
Clinical Evidence http://www.clinicalevidence.com/ceweb/conditions/index.jsp
Health Evidence Bulletins Wales <http://www.uwcm.ac.uk/uwcm/lb/pep>
Centre for Disease Control (Pre-conception pages):
http://www.cdc.gov/ncbddd/preconception/default.htm

Cochrane Database of Systematic Reviews
Via Cochrane Library Issue 2, 2006.
Search date 21st June 2006

32 records retrieved

#1	(preconception or prenatal or prepregnancy) in Title, Abstract or Keywords in Cochrane Reviews
#2	(pre-conception or pre-natal or pre-pregnancy) in Title, Abstract or Keywords in Cochrane Reviews
#3	pre-conceptual or preconceptual in Title, Abstract or Keywords in Cochrane Reviews
#4	peri-concept* or periconcept* in Title, Abstract or Keywords in Cochrane Reviews
#5	((plan* or before or preparing or prepare or preparation or prior or trying) near/3 (pregnancy or pregnant or conceive or conception or conceiving)) in Title, Abstract or Keywords in Cochrane Reviews
#6	(becom* pregnant) or (get pregnant) in Title, Abstract or Keywords in Cochrane Reviews
#7	trying near/3 baby in Title, Abstract or Keywords in Cochrane Reviews
#8	trying near/3 conceive in Title, Abstract or Keywords in Cochrane Reviews
#9	start* near/2 family in Title, Abstract or Keywords in Cochrane Reviews
#10	MeSH descriptor Preconception Care explode all trees in MeSH products
#11	women near/2 reproductive in Title, Abstract or Keywords in Cochrane Reviews
#12	women near/2 childbear* in Title, Abstract or Keywords in Cochrane Reviews
#13	female* near/2 reproductive in Title, Abstract or Keywords in Cochrane Reviews

#14 female* near/2 childbear* in Title, Abstract or Keywords in Cochrane Reviews
#15 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14)
#16 diet* or food* or eat or eats or eaten or eating or nutrition* or fruit* or vegetable* or nutrient* or vitamin* or thiamin or niacin or folate* or micronutrient* or macronutrient* or multivitamin* or folic or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or alcohol* or weight in Title, Abstract or Keywords in Cochrane Reviews
#17 "nicotinic acid" in Title, Abstract or Keywords in Cochrane Reviews
#18 "dietary salt" in Title, Abstract or Keywords in Cochrane Reviews
#19 food near/2 supplement* in Title, Abstract or Keywords or food near/2 fortif* in Title, Abstract or Keywords or food near/2 choice* in Title, Abstract or Keywords in Cochrane Reviews
#20 MeSH descriptor Diet explode all trees in MeSH products
#21 MeSH descriptor Food explode all trees in MeSH products
#22 MeSH descriptor Nutrition explode all trees in MeSH products
#23 MeSH descriptor Nutritional Status explode all trees in MeSH products
#24 MeSH descriptor Diet Therapy explode all trees in MeSH products
#25 MeSH descriptor Fruit explode all trees in MeSH products
#26 MeSH descriptor Vegetables explode all trees in MeSH products
#27 MeSH descriptor Iron, Dietary explode all trees in MeSH products
#28 MeSH descriptor Calcium, Dietary explode all trees in MeSH products
#29 MeSH descriptor Dietary Fats explode all trees in MeSH products
#30 MeSH descriptor Dietary Proteins explode all trees in MeSH products
#31 MeSH descriptor Vitamins explode all trees in MeSH products
#32 MeSH descriptor Zinc explode all trees in MeSH products
#33 MeSH descriptor Magnesium explode all trees in MeSH products
#34 MeSH descriptor Selenium explode all trees in MeSH products
#35 MeSH descriptor Sodium, Dietary explode all trees in MeSH products
#36 MeSH descriptor Alcoholic Beverages explode all trees in MeSH products
#37 MeSH descriptor Alcohol Drinking explode all trees in MeSH products
#38 MeSH descriptor Energy Intake explode all trees in MeSH products
#39 MeSH descriptor Riboflavin explode all trees in MeSH products
#40 MeSH descriptor Pyridoxine explode all trees in MeSH products
#41 MeSH descriptor Folic Acid explode all trees in MeSH products
#42 MeSH descriptor Body Mass Index explode all trees in MeSH products
#43 MeSH descriptor Prenatal Nutrition explode all trees in MeSH products
#44 MeSH descriptor Maternal Nutrition explode all trees in MeSH products
#45 (#16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44)
#46 #15 and #45

DARE
http://www.york.ac.uk/inst/crd/crddatabases.htm

using CRD's CARS software interface
search date = 21/6/06

records retrieved = 29

Search strategy

S preconception or prenatal or prepregnancy
S pre(w)conception or pre(w)natal or pre(w)pregnancy
S preconceptual or pre(w)conceptual
S periconcept$ or peri(w)concept$
S (plan$ or before or preparing or prepare or preparation or prior or trying)(3w)(pregnancy or pregnant or conceive or conception or conceiving)
S become$(w)pregnant
S get$(w)pregnant
S trying(3w)baby
S trying(3w)conceive
S starting(2w)family
S women(2w)reproductive
S women(2w)childbear$
S female$(2w)childbear$
S female$(2w)reproductive
S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14
S diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin$ or thiamine or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or folic or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or alcohol$ or weight
S nicotinic(w)acid
S dietary(w)salt
S calcium or protein$ or sodium
S energy(w)intake
S body(w)mass(w)index
S s16 or s17 or s18 or s19 or s20 or s21
S s15 and s22
S 1/xno or 2/xno or 10/xno or 12/xno
S s23 and s24

Health Technology Assessment database
http://www.york.ac.uk/inst/crd/crddatabases.htm

using CRD's CAIRS software interface
search date 21/6/06

4 records retrieved

S preconception or prenatal or prepregnancy
S pre(w)conception or pre(w)natal or pre(w)pregnancy
S preconceptual or pre(w)conceptual
S periconcept$ or peri(w)concept$
S (plan$ or before or preparing or prepare or preparation or prior or trying)(3w)(pregnancy or pregnant or conceive or conception or conceiving)
S become$(w)pregnant
S get$(w)pregnant
S trying(3w)baby
S trying(3w)conceive
S starting(2w)family
S women(2w)reproductive
S women(2w)childbear$
S female$(2w)childbear$
S female$(2w)reproductive
S s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9 or s10 or s11 or s12 or s13 or s14

S diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin$ or thiamine or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or folic or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or alcohol$ or weight
S nicotinic(w)acid
S dietary(w)salt
S calcium or protein$ or sodium
S energy(w)intake
S body(w)mass(w)index
S s16 or s17 or s18 or s19 or s20 or s21
S s15 and s22

Ongoing Reviews Register
Via the National Research Register
http://www.nrr.nhs.uk
Issue 2, 2006

Search date 22nd June 2006

No ongoing reviews were identified

Search strategy

#1 (preconception or prenatal or prepregnancy)
#2 (pre-conception or pre-natal or pre-pregnancy)
#3 (pre-conceptual or preconceptual or peri-concept* or periconcept*)
#4 (plan* next pregnan*)
#5 (plan* next conceiv*)
#6 (plan* next concept*)
#7 (plan* near conceiv*)
#8 (plan* near pregnan*)
#9 (before near pregnan*)
#10 (before near conceiv*)
#11 (before near concept*)
#12 (prepar* near pregnan*)
#13 (prepar* near conceiv*)
#14 (prepar* near concept*)
#15 (prior near pregnan*)
#16 (prior near conceiv*)
#17 (prior near concept*)
#18 (trying near pregnan*)
#19 (trying near conceiv*)
#20 (trying near concept*)
#21 (becom* next pregnan*)
#22 (get* next pregnan*)
#23 (trying near baby)
#24 (trying near conceive)
#25 (start* near family)
#26 PRECONCEPTION CARE explode all trees (MeSH)
#27 (women near (reproductive next age))
#28 (women near childbear*)
#29 (female* near (reproductive next age))
#30 (female* near childbear*)
#31 (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10)

#32 (#11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20)
#33 (#21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#34 (#31 or #32 or #33)
#35 (diet* or food* or eat or eats or eating or nutrition* or fruit* or vegtable* or nutrient* or vitamin* or thimain or niacin or folate* or micronutrient* or macronutrient* or multivitamin* or folic or magnesium or selnium or zinc or caffeine or pyridoxine or riboflavin or alcohol* or weight)
#36 (selenium or vegetable*)
#37 (nicotinic next acid*)
#38 (dietary next salt*)
#39 DIET explode all trees (MeSH)
#40 FOOD explode all trees (MeSH)
#41 NUTRITION explode all trees (MeSH)
#42 NUTRITIONAL STATUS explode all trees (MeSH)
#43 DIET THERAPY explode all trees (MeSH)
#44 FRUIT explode all trees (MeSH)
#45 VEGETABLES explode all trees (MeSH)
#46 IRON DIETARY explode all trees (MeSH)
#47 CALCIUM DIETARY explode all trees (MeSH)
#48 DIETARY FATS explode all trees (MeSH)
#49 DIETARY PROTEINS explode all trees (MeSH)
#50 VITAMINS explode all trees (MeSH)
#51 ZINC explode all trees (MeSH)
#52 MAGNESIUM explode all trees (MeSH)
#53 SELENIUM explode all trees (MeSH)
#54 SODIUM DIETARY explode all trees (MeSH)
#55 ALCOHOLIC BEVERAGES explode all trees (MeSH)
#56 ALCOHOL DRINKING explode all trees (MeSH)
#57 ENERGY INTAKE explode all trees (MeSH)
#58 RIBOFLAVIN explode all trees (MeSH)
#59 PYRIDOXINE explode all trees (MeSH)
#60 FOLIC ACID explode all trees (MeSH)
#61 BODY MASS INDEX explode all trees (MeSH)
#62 PRENATAL NUTRITION explode all trees (MeSH)
#63 MATERNAL NUTRITION explode all trees (MeSH)
#64 (#35 or #36 or #37 or #38 or #39)
#65 (#40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49)
#66 (#50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59)
#67 (#60 or #61 or #62 or #63)
#68 (#64 or #65 or #66 or #67)
#69 (#34 and #68)

Stage two of the literature searching was to identify RCTs using the following databases : MEDLINE, EMBASE, CENTRAL, CINAHL, PsycINFO and MIDIRS On-Line. Details of search strategies are given below.

MEDLINE
Via Ovid
1990 to June week 2 2006

Search date 27th June 2006

751 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp Preconception Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12
14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/
19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetables/
23 exp iron, dietary/
24 exp calcium, dietary/
25 exp dietary fats/
26 exp dietary proteins/
27 exp vitamins/
28 exp zinc/
29 exp magnesium/
30 exp selenium/
31 exp sodium, dietary/
32 exp alcoholic beverages/
33 alcohol drinking/
34 exp energy intake/
35 exp nicotinic acid/
36 exp riboflavin/
37 exp pyridoxine/
38 exp folic acid/
39 body mass index/
40 or/ 14-39
41 13 and 40
42 exp prenatal nutrition/
43 exp maternal nutrition/
44 41 or 42 or 43
45 RANDOMIZED CONTROLLED TRIAL.pt.
46 CONTROLLED CLINICAL TRIAL.pt.
47 RANDOMIZED CONTROLLED TRIALS.sh.
48 RANDOM ALLOCATION.sh.
49 DOUBLE BLIND METHOD.sh.

50 SINGLE BLIND METHOD.sh.
51 or/ 45-50
52 (ANIMALS not HUMAN).sh.
53 51 not 52
54 CLINICAL TRIAL.pt.
55 exp CLINICAL TRIALS/
56 (clin$ adj25 trial$).ti,ab.
57 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
58 PLACEBOS.sh.
59 placebo$.ti,ab.
60 random$.ti,ab.
61 RESEARCH DESIGN.sh.
62 or/ 54-61
63 62 not 52
64 63 not 53
65 53 or 64
66 44 and 65
67 exp africa/ or exp caribbean region/ or exp central america/ or exp latin america/ or exp south america/ or exp asia/
68 66 not 67
69 limit 68 to yr="1990 - 2006"

EMBASE
Via Ovid
1990 to 2006 week 25

Search date 27th June 2006

1021 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp maternal Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12
14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/

19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetable/
23 exp iron intake/
24 exp calcium intake/
25 exp fat intake/
26 exp protein intake/
27 exp vitamin/
28 exp zinc/
29 exp magnesium/
30 exp selenium/
31 exp sodium/
32 exp alcoholic beverages/
33 exp mineral intake/
34 exp caloric intake/
35 exp nicotinic acid/
36 exp riboflavin/
37 exp pyridoxine derivative/
38 exp folic acid/
39 body mass/
40 or/ 14-39
41 13 and 40
42 exp maternal nutrition/
43 41 or 42
44 clinical trial/
45 randomized controlled trial/
46 randomization/
47 single blind procedure/
48 double blind procedure/
49 crossover procedure/
50 placebo/
51 randomi?ed controlled trial$.tw.
52 rct.tw.
53 random allocation.tw.
54 randomly allocated.tw.
55 allocated randomly.tw.
56 (allocated adj2 random).tw.
57 single blind$.tw.
58 double blind$.tw.
59 ((treble or triple) adj blind$).tw.
60 placebo$.tw.
61 prospective study/
62 or/44-61
63 case study/
64 case report.tw.
65 abstract report/ or letter/
66 or/ 63-65
67 62 not 66
68 43 and 67
69 exp africa/ or exp central america/ or exp south america/ or exp asia/
70 68 not 69
71 limit 70 to yr="1990 - 2006"

CENTRAL
Via Cochrane Library Issue 2 2006

Search date 29th June 2006

542 records retrieved

#1 (preconception or prenatal or prepregnancy):ti,ab,kw or (pre-conception or pre-natal or pre-pregnancy):ti,ab,kw or (preconceptual or periconcept*):ti,ab,kw or (pre-conceptual or peri-concept*):ti,ab,kw or ((plan* or before or preparing or prepare or preparation or prior or trying) near/3 (pregnancy or pregnant or conceive or conception or conceiving)):ti,ab,kw in Clinical Trials
#2 (becom* pregnant):ti,ab,kw or (get* pregnant):ti,ab,kw or (trying near/3 baby):ti,ab,kw or (trying near/3 conceive):ti,ab,kw or (start* near/3 family):ti,ab,kw in Clinical Trials
#3 MeSH descriptor Preconception Care explode all trees
#4 (women near/2 reproductive):ti,ab,kw or (women near/2 childbear*):ti,ab,kw or (female* near/2 reproductive):ti,ab,kw or (female near/2 childbear*):ti,ab,kw in Clinical Trials
#5 (#1 OR #2 OR #3 OR #4)
#6 (diet* or food* or eat or eats or eaten or eating or nutrition* or fruit* or vegetable* or nutrient* or thiamin or niacin or folate* or micronutrient* or macronutrient* or multivitamin* or vitamin* or folic or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol* or weight):ti,ab,kw in Clinical Trials
#7 MeSH descriptor Diet explode all trees
#8 MeSH descriptor Food explode all trees
#9 MeSH descriptor Nutrition explode all trees
#10 MeSH descriptor Nutritional Status explode all trees
#11 MeSH descriptor Diet Therapy explode all trees
#12 MeSH descriptor Fruit explode all trees
#13 MeSH descriptor Vegetables explode all trees
#14 MeSH descriptor Iron, Dietary explode all trees
#15 MeSH descriptor Calcium, Dietary explode all trees
#16 MeSH descriptor Dietary Fats explode all trees
#17 MeSH descriptor Dietary Proteins explode all trees
#18 MeSH descriptor Vitamins explode all trees
#19 MeSH descriptor Zinc explode all trees
#20 MeSH descriptor Magnesium explode all trees
#21 MeSH descriptor Selenium explode all trees
#22 MeSH descriptor Sodium, Dietary explode all trees
#23 MeSH descriptor Alcoholic Beverages explode all trees
#24 MeSH descriptor Alcohol Drinking explode all trees
#25 MeSH descriptor Energy Intake explode all trees
#26 MeSH descriptor Niacin explode all trees
#27 MeSH descriptor Pyridoxine explode all trees
#28 MeSH descriptor Folic Acid explode all trees
#29 MeSH descriptor Body Mass Index explode all trees
#30 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29)
#31 (#5 AND #30)
#32 MeSH descriptor Prenatal Nutrition explode all trees
#33 MeSH descriptor Maternal Nutrition explode all trees
#34 (#31 OR #32 OR #33)

#35 (#34), from 1990 to 2006
#36 MeSH descriptor Africa explode all trees
#37 MeSH descriptor Caribbean Region explode all trees
#38 MeSH descriptor Central America explode all trees
#39 MeSH descriptor Latin America explode all trees
#40 MeSH descriptor South America explode all trees
#41 MeSH descriptor Asia explode all trees
#42 (#36 OR #37 OR #38 OR #39 OR #40 OR #41)
#43 (#35 AND NOT #42)

CINAHL
Via Ovid
1990 to June week 3 2006

Search date 27th June 2006

110 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp Prepregnancy Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12
14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/
19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetables/
23 exp iron compounds/
24 exp calcium, dietary/
25 exp dietary fats/
26 exp dietary proteins/
27 exp vitamins/
28 exp zinc compounds/
29 exp magnesium compounds/
30 exp selenium compounds/

31 exp sodium chloride, dietary/
32 exp alcoholic beverages/
33 exp energy intake/
34 exp niacin/
35 exp riboflavin/
36 exp pyridoxine/
37 exp folic acid/
38 body mass index/
39 or/ 14-38
40 13 and 39
41 exp clinical trials/
42 clinical trial.pt.
43 (clinic$ adj trial$1).tw.
44 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
45 randomi?ed control$ trial$.tw.
46 random assignment/
47 random$ allocat$.tw.
48 placebo$.tw.
49 placebos/
50 quantitative studies/
51 allocat$ random$.tw.
52 or/ 41-51
53 40 and 52
54 exp africa/ or exp asia/ or exp south america/ or exp central america/
55 53 not 54
56 limit 55 to yr="1990 - 2006"

PSYCINFO
Via Ovid
1990 to June week 3 2006

Search date 27th June 2006

982 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
12 or/ 1-11
13 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.

14 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
15 exp diets/
16 exp food/
17 exp nutrition/
18 exp fruit/
19 exp iron/
20 exp calcium/
21 exp proteins/
22 exp vitamins/
23 exp zinc/
24 exp magnesium/
25 exp sodium/
26 exp alcoholic beverages/
27 exp nicotinic acid/
28 exp folic acid/
29 body weight/
30 or/ 13-29
31 12 and 30
32 limit 31 to yr="1990 - 2007"
33 limit 32 to human

MIDIRS On-Line

https://www.midirs.org/midirs/midIA.nsf/welcome?openform&id=5692AF3F8432A7FA802571A1003E181A

Search date= 4th July 2006

The MIDIRS On-Line service does not allow complex searches to be undertaken. It does offer, however, a number of "standard searches" i.e. a pre-defined search strategy that the database user can run. A number of these seemed to be of relevance to the review i.e.

Folic acid – health education	(P115)	130 records
Folic acid	(P57)	219 records
Prepregnancy care	(P22)	135 records
Diet and nutrition in pregnancy	(P42)	261 records
Diet and nutrition in pregnancy	(P42A)	232 records
Diet and nutrition in pregnancy	(P42B)	100 records

These searches were run and the results were downloaded as page web pages for the reviewers to scan.

Stage three of the literature searching to identify other corroborative evidence was to search MEDLINE, EMBASE, CINAHL using the strategies as listed below.

MEDLINE

Via Ovid
1966 to July week 2 2006

Search date 25th July 2006

482 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp Preconception Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12
14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/
19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetables/
23 exp iron, dietary/
24 exp calcium, dietary/
25 exp dietary fats/
26 exp dietary proteins/
27 exp vitamins/
28 exp zinc/
29 exp magnesium/
30 exp selenium/
31 exp sodium, dietary/
32 exp alcoholic beverages/
33 alcohol drinking/
34 exp energy intake/
35 exp nicotinic acid/
36 exp riboflavin/
37 exp pyridoxine/
38 exp folic acid/
39 body mass index/
40 or/ 14-39
41 13 and 40
42 exp prenatal nutrition/
43 exp maternal nutrition/
44 41 or 42 or 43
45 RANDOMIZED CONTROLLED TRIAL.pt.
46 CONTROLLED CLINICAL TRIAL.pt.
47 RANDOMIZED CONTROLLED TRIALS.sh.

48 RANDOM ALLOCATION.sh.
49 DOUBLE BLIND METHOD.sh.
50 SINGLE BLIND METHOD.sh.
51 or/ 45-50
52 (ANIMALS not HUMAN).sh.
53 51 not 52
54 CLINICAL TRIAL.pt.
55 exp CLINICAL TRIALS/
56 (clin$ adj25 trial$).ti,ab.
57 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
58 PLACEBOS.sh.
59 placebo$.ti,ab.
60 random$.ti,ab.
61 RESEARCH DESIGN.sh.
62 or/54-61
63 62 not 52
64 63 not 53
65 53 or 64
66 44 not 65
67 (systematic review or meta-analysis).ti. or meta-analysis.pt.
68 66 not 67
69 animals/
70 humans/
71 69 not (69 and 70)
72 68 not 71
73 letter.pt.
74 editorial.pt.
75 comment.pt.
76 73 or 74 or 75
77 72 not 76
78 exp africa/ or exp caribbean region/ or exp central america/ or exp latin america/ or exp south america/ or exp asia/
79 77 not 78
80 exp great britain/
81 (england or scotland or wales or ireland or united kingdom or uk or britain).ti,ab,in.
82 (english or irish or scottish or welsh or british).ti,ab.
83 80 or 81 or 82
84 79 and 83
85 limit 84 to yr="1990 - 2006"

EMBASE

Via Ovid
1980 to 2006 WEEK 29

Search date 25th July 2006

529 records retrieved

(preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.

4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp maternal Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12
14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/
19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetable/
23 exp iron intake/
24 exp calcium intake/
25 exp fat intake/
26 exp protein intake/
27 exp vitamin/
28 exp zinc/
29 exp magnesium/
30 exp selenium/
31 exp sodium/
32 exp alcoholic beverages/
33 exp mineral intake/
34 exp caloric intake/
35 exp nicotinic acid/
36 exp riboflavin/
37 exp pyridoxine derivative/
38 exp folic acid/
39 body mass/
40 or/ 14-39
41 13 and 40
42 exp maternal nutrition/
43 41 or 42
44 clinical trial/
45 randomized controlled trial/
46 randomization/
47 single blind procedure/
48 double blind procedure/
49 crossover procedure/
50 placebo/
51 randomi?ed controlled trial$.tw.
52 rct.tw.

53 random allocation.tw.
54 randomly allocated.tw.
55 allocated randomly.tw.
56 (allocated adj2 random).tw.
57 single blind$.tw.
58 double blind$.tw.
59 ((treble or triple) adj blind$).tw.
60 placebo$.tw.
61 prospective study/
62 or/ 44-61
63 case study/
64 case report.tw.
65 abstract report/ or letter/
66 or/ 63-65
67 62 not 66
68 43 not 67
69 "systematic review"/
70 meta analysis/
71 (systematic review or meta-analysis).ti,ab.
72 69 or 70 or 71
73 68 not 72
74 exp africa/ or exp central america/ or exp south america/ or exp asia/
75 73 not 74
76 exp united kingdom/
77 (england or scotland or wales or ireland or great britain or uk or britain).ti,ab,in.
78 (english or irish or scottish or welsh or british).ti,ab.
79 76 or 77 or 78
80 75 and 79
81 limit 80 to yr="1990 - 2007"

CINAHL

Via Ovid
1982 to July week 3 2006

Search date 25th July 2006

79 records retrieved

1 (preconception or prenatal or prepregnancy).ti,ab,de.
2 (pre-conception or pre-natal or pre-pregnancy).ti,ab,de.
3 pre-conceptual.ti,ab,de.
4 preconceptual.ti,ab,de.
5 peri-concept$.ti,ab,de.
6 periconcept$.ti,ab,de.
7 ((plan$ or before or preparing or prepare or preparation or prior or trying) adj3 (pregnancy or pregnant or conceive or conceiving or conception)).ti,ab,de.
8 ((becom$ or get$) adj pregnant).ti,ab,de.
9 (trying adj3 (baby or conceive)).ti,ab,de.
10 (start$ adj2 family).ti,ab,de.
11 exp Prepregnancy Care/
12 ((women adj2 reproductive age) or (women adj2 childbear$) or (female$ adj2 reproductive age) or (female$ adj2 childbear$)).ti,ab,de.
13 or/ 1-12

14 (diet$ or food$ or eat or eats or eaten or eating or nutrition$ or fruit$ or vegetable$ or nutrient$ or vitamin C or thiamin or niacin or folate$ or micronutrient$ or macronutrient$ or multivitamin$ or vitamin$ or folic acid or magnesium or selenium or zinc or caffeine or pyridoxine or riboflavin or nicotinic acid or dietary salt or alcohol$ or weight).ti,ab,de.
15 (food adj2 (supplement$ or fortif$ or choice$)).ti,ab,de.
16 exp diet/
17 exp food/
18 exp nutrition/
19 exp nutritional status/
20 exp diet therapy/
21 exp fruit/
22 exp vegetables/
23 exp iron compounds/
24 exp calcium, dietary/
25 exp dietary fats/
26 exp dietary proteins/
27 exp vitamins/
28 exp zinc compounds/
29 exp magnesium compounds/
30 exp selenium compounds/
31 exp sodium chloride, dietary/
32 exp alcoholic beverages/
33 exp energy intake/
34 exp niacin/
35 exp riboflavin/
36 exp pyridoxine/
37 exp folic acid/
38 body mass index/
39 or/ 14-38
40 13 and 39
41 exp clinical trials/
42 clinical trial.pt.
43 (clinic$ adj trial$1).tw.
44 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw.
45 randomi?ed control$ trial$.tw.
46 random assignment/
47 random$ allocat$.tw.
48 placebo$.tw.
49 placebos/
50 quantitative studies/
51 allocat$ random$.tw.
52 or/ 41-51
53 40 not 52
54 "Systematic Review"/
55 Meta Analysis/
56 (systematic review or meta-analysis).ti,ab.
57 54 or 55 or 56
58 53 not 57
59 exp africa/ or exp asia/ or exp south america/ or exp central america/
60 58 not 59
61 exp great britain/
62 (england or scotland or wales or ireland or united kingdom or uk or britain).ti,ab,in.
63 (english or irish or scottish or welsh or british).ti,ab.

64 61 or 62 or 63
65 60 and 64
66 limit 65 to yr="1990 - 2006"

Results from the update search – 5th February 2007

Results file	Number of new records before deduplication	Number of new records after deduplication against original Endnote library
Reviews: **CDSR** **DARW** **HTA** **NRR**	**15**	**15**
RCTs: **MEDLINE** **EMBASE** **CINAHL** **PsychINFO** **CENTRAL**	**299**	**253**
Other studies: **MEDLINE** **EMBASE** **CINAHL**	**115**	**78**

APPENDIX D - Methodology Checklist

From: National Institute for Health and Clinical Excellence (2006). *Methods for development of NICE public health guidance.* London: National Institute for Health and Clinical Excellence. Available from: www.nice.org.uk

Notes on the use of methodology checklist: systematic reviews

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully, and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study. For each question in this section you should use one of the following to indicate how well it has been addressed in the review.
Well covered
Adequately addressed
Poorly addressed
Not addressed (that is, not mentioned, or indicates that this aspect of study design was ignored)
Not reported (that is, mentioned, but insufficient detail to allow assessment to be made)
Not applicable

The study addresses an appropriate and clearly focused question

Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

A description of the methodology used is included

One of the key distinctions between a systematic review and a general review is the
systematic methodology used. A systematic review should include a detailed description of the methods used to identify and evaluate individual studies. If this description is not present, it is not possible to make a thorough evaluation of the quality of the review, and it should be rejected as a source of level 1 evidence **(though it may be useable as level 4 evidence, if not better evidence can be found).**

The literature search is sufficiently rigorous to identify all the relevant studies

A systematic review based on a limited literature search – for example, one limited to Medline only – is likely to be heavily biased. A well-conducted review should as a minimum look at Embase and Medline, and from the late 1990s onward, the Cochrane Library. Any indication that hand searching of key journals, or follow up of reference lists of included studies were carried out in addition to electronic database searches can normally be taken as evidence of a well-conducted review.

Study quality is assessed and taken into account

A well-conducted systematic review should have used clear criteria to assess whether individual studies had been well conducted before deciding whether to include or exclude them. If there is not indication of such an assessment, the review should be rejected as a source of level 1 evidence**. If details of the assessment are poor, or the methods are considered to be inadequate, the quality of the review should be downgraded. In either case, it may be worthwhile obtaining and evaluating the individual studies as part of the review you are conducting for this guideline.**

There are enough similarities between the studies selected to make combining them reasonable

Studies covered by a systematic review should be selected using clear inclusion criteria. These criteria should include, either implicitly or explicitly, the question of whether the selected studies can legitimately be compared. It should be clearly ascertained, for example, that the populations covered by the studies are comparable, that the methods used in the investigations are the same, that the outcome measures are comparable and the variability in effect sized between studies is not greater than would be expected by chance alone.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.
The aim of the other two questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Methodology checklist for systematic reviews

First author/year

Section 1: Internal validity

	In a well-conducted SR:	**In this study this criterion is: (copy one option into your column with comment if required)**	Reviewer 1 (initials)	Reviewer 2 (initials)
1.1	The study addresses an appropriate and clearly focused question	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.2	A description of the methodology used is included.	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.3	The literature search is sufficiently rigorous to identify all the relevant studies.	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.4	Study quality is assessed and taken into account.	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.5	There are enough similarities between the studies selected to make combining them reasonable.	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		

Section 2: Overall assessment of the study

2.1	How well was the study done to minimise bias? Code ++, + or -	Reviewer 1 (initials) Comment if desired	Reviewer 2 (initials) Comment if desired	Reviewer 3 (initials) Agreed
2.2	If coded as + or – what is the likely direction in which bias might affect the study results?			
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain the overall effect is due to the study intervention?			
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?			

Notes on the use of methodology checklist: randomised controlled trials

Section 1 identifies the study and asks a series of questions aimed at establishing the internal validity of the study under review – that is, making sure that it has been carried out carefully, and that the outcomes are likely to be attributable to the intervention being investigated. Each question covers an aspect of methodology that research has shown makes a significant difference to the conclusions of a study.
For each question in this section you should use one of the following to indicate how well it has been addressed in the study.
Well covered
Adequately addressed
Poorly addressed
Not addressed (that is, not mentioned, or indicates that this aspect of study design was ignored)
Not reported (that is, mentioned, but insufficient detail to allow assessment to be made)
Not applicable

The study addresses an appropriate and clearly focused question

Unless a clear and well-defined question is specified, it will be difficult to assess how well the study has met its objectives or how relevant it is to the question you are trying to answer on the basis of its conclusions.

The assignment of subjects to treatment groups is randomised.

Random allocation of patients to receive one or other of the treatments under investigation, or to receive either treatment or placebo, is fundamental to this type of study. **If there is no indication of randomisation, the study should be rejected.** If the description of randomisation is poor, or the process used is not truly random (for example, allocation by date, alternating between one group and another) or can otherwise be seen as flawed, the study should be given a lower quality rating.

An adequate concealment method is used.

Research has shown that where allocation concealment is inadequate, investigators can overestimate the effect of interventions by up to 40%. Centralised allocation, computerised allocation systems or the use of coded identical containers would all be regarded as adequate methods of concealment, and may be taken as indicators of a well-conducted study. If the method of concealment used is regarded as poor, or relatively easy to subvert, the study must be given a lower quality rating, and can be rejected if the concealment method is seen as inadequate.B.2.4Subjects and investigators are kept ‘blind’ about treatment allocation.
Blinding can be carried out up to three levels. In single-blind studies, patients are unaware of which treatment they are receiving; in double-blind studies the doctor and the patient are unaware of which treatment the patient is receiving; in triple-blind studies patients, healthcare providers and those conducting the analysis are unaware of which patients received which treatment. The higher the level of blinding, the lower the risk of bias in the study.

The treatment and control groups are similar at the start of the trial.

Patients selected for inclusion in a trial should be as similar as possible, in order to eliminate any possible bias. The study should report any significant differences in the composition of the study groups in relation to gender mix, age, stage of disease (if

appropriate), social background, ethnic origin or comorbid conditions. These factors may be covered by inclusion and exclusion criteria, rather than being reported directly. Failure to address this question, or the use of inappropriate groups, should lead to the study being downgraded.

The only difference between groups is the treatment under investigation.

If some patients received additional treatment, even if of a minor nature or consisting of advice and counselling rather than a physical intervention, this treatment is a potential confounding factor that may invalidate the results. **If groups were *not* treated equally, the study should be rejected unless no other evidence is available.** If the study *is* used as evidence it should be treated with caution, and given a low quality rating.

All relevant outcomes measured in a standard, valid and reliable way.

If some significant clinical outcomes have been ignored, or not adequately taken into account, the study should be downgraded. It should also be downgraded if the measures used are regarded as being doubtful in any way, or applied inconsistently.

What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?

The number of patients that drop out of a study should give concern if the number is very high. Conventionally, a 20% drop-out rate is regarded as acceptable, but this may vary. Some regard should be paid to *why* patients dropped out, as well as how many. It should be noted that the drop-out rate may be expected to be higher in studies conducted over a long period of time. A higher drop-out rate will normally lead to downgrading, rather than rejection of a study.

All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention-to-treat analysis).

In practice, it is rarely the case that all patients allocated to the intervention group receive the intervention throughout the trial, or that all those in the comparison group do not. Patients may refuse treatment, or contra-indications arise that lead them to be switched to the other group. If the comparability of groups through randomisation is to be maintained, however, patient outcomes *must* be analysed according to the group to which they were originally allocated, irrespective of the treatment they actually received. (This is known as *intention-to-treat* analysis.) If it is clear that analysis was not on an intention-to-treat basis, the quality of the study should be downgraded.

Where the study is carried out at more then one site, results are comparable for all sites.

In multi-site studies, confidence in the results should be increased if it can be shown that similar results were obtained at the different participating centres.

Section 2 relates to the overall assessment of the paper. It starts by rating the methodological quality of the study, based on your responses in Section 1 and using the following coding system:

++	All or most of the criteria have been fulfilled. Where they have not been fulfilled the conclusions of the study or review are thought **very unlikely** to alter.
+	Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are

	thought **unlikely** to alter the conclusions.
–	Few or no criteria fulfilled. The conclusions of the study are thought **likely or very likely** to alter.

The code allocated here, coupled with the study type, will decide the **level of evidence** that this study provides.
The aim of the other two questions in this section is to summarise your view of the quality of this study and its applicability to the patient group targeted by the guideline you are working on.

Methodology checklist for RCTs

First author/year

Section 1: Internal validity

	In a well-conducted RCT study:	**In this study this criterion is: (copy one option into your column with comment if required)**	Reviewer 1 (initials)	Reviewer 2 (initials)
1.1	The study addresses an appropriate and clearly focused question	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.2	The assignment of subjects to treatment groups is randomised	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.3	An adequate concealment method is used	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.4	Subjects and investigators are kept 'blind' about treatment allocation	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.5	The treatment and control groups are similar at the start of the trial	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.6	The only difference between groups is the treatment under investigation	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.7	All relevant outcomes are measured in a standard, valid way	Well covered Adequately addressed Poorly addressed Not addressed Not reported		

		Not applicable		
1.8	What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?	Where available, Reviewer 1 report and Reviewer 2 check: Number randomised into each arm Number in each arm with outcome data at the end of the trial Dropout rate (%) for each arm Dropout rate (%) overall		
1.9	All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis, ITT)	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		
1.10	Where the study is carried out at more than one site, results are comparable for all sites	Well covered Adequately addressed Poorly addressed Not addressed Not reported Not applicable		

Section 2: Overall assessment of the study

2.1	How well was the study done to minimise bias? Code ++, + or -	Reviewer 1 (initials) Comment if desired	Reviewer 2 (initials) Comment if desired	(Reviewer 3) Agreed
2.2	If coded as + or – what is the likely direction in which bias might affect the study results?			
2.3	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, are you certain the overall effect is due to the study intervention?			
2.4	Are the results of this study directly applicable to the patient group targeted by this guideline?			

Level and quality of evidence

The following checklist was used to determine the level and quality of evidence of all included studies

Type and quality of evidence	
1^{++}	High quality meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a very low risk of bias
1^{+}	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs (including cluster RCTs) with a high risk of bias
2^{++}	High quality systematic reviews of these types of studies, or individual, non-RCTs, case-control studies, cohort studies, CBA studies, ITS, and correlation studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well conducted non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Non-RCTs, case-control studies, cohort studies, CBA studies, ITS and correlation studies with a high risk – or chance – of confounding bias, and a significant risk that the relationship is not causal
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

APPENDIX E – Non-UK, non-RCT studies

The search results for worldwide randomised control trials and UK studies found eleven papers reporting studies that were not randomised control trials and were undertaken outside the UK. These studies were excluded from the review but are described in this Appendix for the interested reader. Nine studies are about folic acid (FA) (Amitai 2004, Bower 2005, Busby 2005, Byrne 2003, Chacko 2003, Egen 2003, Lawrence 2003, Watson 2006, Williams 2001), and two describe nutritional interventions (Dubois 1997, Widga 1999).

Folic acid (n=9)

The nine studies about folic acid (FA) took place between 2001 and 2006. Three were undertaken in Europe (Byrne 2003, Egen 2003, Busby 2005), one in Israel (Amitai 2004), three in Australia (Williams 2001, Bower 2005, Watson 2006) and two in the USA (Chacko 2003, Lawrence 2003). Five were before-after studies without control groups (Byrne 2003, Egen 2003, Amitai 2004, Williams 2001, Chacko 2003), one was a described as an interrupted time series design (Lawrence 2003) and three were surveys (Busby 2005, Bower 2005, Watson 2006).

Lawrence (2003) reported a study using an interrupted time series design where the intervention occurred at a clearly defined point in time, but only one data point was recorded before and one after the intervention. This study therefore does not meet the minimum criteria for time series studies where there is a change in trend attributable to the intervention, according to Methodology checklist: Interrupted time series (EPOC version) (*Methods for development of NICE public health guidance* March 2006 pp 101-2 (NICE methods manual)). Checklists for the methodologies used in the other eight studies are not currently included in the NICE methods manual and these studies have not been quality appraised.

One survey (Busby 2005) covers 18 countries in Europe using data from population-based registries. Two before-after studies report national campaigns, one in Israel among women attending maternal and child health clinics (Amitai 2004) and one in Australia among women of childbearing age (Williams 2001). Three studies were regional, one in Western Australia with recently pregnant women (Bower 2005), another Australian study included two surveys, one of recent mothers in Victoria and the other of mothers of infants <12 months old in New South Wales (Watson 2006) and another in Southern California with women of childbearing age who were members of a health plan (Lawrence 2003). Two took place in large cities; Chacko (2003) studied young, ethnic minority women seeking free and confidential services at reproductive health clinics in a large city in Texas, and Egen (2003) included gynaecologists, pharmacists and women during their postnatal hospital stay in Munich. Byrne (2003) studied 100 women living on the island of Ireland who were aunts or cousins of a child born with a neural tube defect (NTD) (Byrne 2003).

The interventions aimed to increase knowledge and uptake of FA and had a wide range of components, generally including leaflets and posters, and also vouchers (Byrne 2003), personalised letters to gynaecologists and personal visits to pharmacists (Egen 2003), training sessions and seminars, national and regional media campaigns (Amitai 2004, Williams 2001, Bower 2005), and giving a supply of supplements to women (Byrne 2003, Chacko 2003, Lawrence 2003). Specific education for professionals was part of the intervention in the studies by Bower (2005) Amitai (2004) Egen (2003) and Lawrence (2003), and personalised education for women was part of the intervention provided by Chacko (2005). Williams (2001) compared FA awareness after two different advertisements, first without and then with the specific health message that FA prevents NTDs. Lawrence (2003) assessed both provider education

and direct mailing of multivitamin tablets to women. Information in Lawrence's study was provided in English and Spanish but did not specifically include the message that FA prevents NTDs. The national campaign in Israel (Amitai 2004) provided information in Hebrew, Arabic and Russian with special emphasis on taking FA supplements for 3 months before and after conception. Amitai (2004) also notes that >90% of marriages in Israel are religious, and all religious leaders were asked to give FA information to couples registering for marriage. In addition, FA information was distributed to all *mikvaot* (post-menstrual ritual baths). Busby (2005) and Watson (2006) report surveys which do not include an intervention. However, Watson (2006) found in a survey in Victoria, Australia, that recent mothers reported that their general practitioner or obstetrician was the source of information about folate, followed by 45% mothers citing family or friends as the source.

The main outcomes reported were changes in knowledge and use of FA supplements. Knowledge increased among women ($p<0.05$), and more gynaecologists said they recommended FA to women ($p<0.05$) after Egen's intervention in Munich (2003). Awareness and correct knowledge both increased ($p<0.001$) after the national campaign in Israel (Amitai 2004). In Williams' study in Australia, awareness increased 8% with the basic advertisement and by a further 15% when the specific health claim that FA prevents NTDs was included. Use of FA among relatives of children in Ireland with an NTD increased ($p<0.05$) (Byrne 2003). Bower (2005) found 62% of the recent mothers surveyed in Western Australia knew about preconceptional FA, 29% took FA tablets periconceptionally, and 57% obtained periconceptional FA from fortified foods. Watson (2006) found higher levels in Victoria and New South Wales: 76% recent mothers surveyed in Victoria knew about preconceptional FA; 36% recent mothers in Victoria and 46% recent mothers in New South Wales took FA tablets periconceptionally. Additionally, Watson found that 8% mothers in Victoria increased their periconceptional dietary folate intake and 28% mothers in New South Wales. Uptake of multivitamins with FA in Chacko's study (2003) was 9% before the intervention, and 3 months after individual instruction 76% were found to be taking the tablets. Lawrence (2003) found a small, temporary increase ($p<0.006$) in uptake of FA only among those mailed tablets. The only intervention that appeared to result in a large increase in use of FA supplements ($p<0.001$) was the national campaign in Israel (Amitai 2004).

Six studies (Byrne 2003, Egen 2003, Amitai 2004, Williams 2001, Bower 2005 and Watson 2006) found use of FA supplements was directly related to socioeconomic status; the remaining three studies did not make this comparison. One Australian survey in Victoria found multiparous women were significantly less likely to take periconceptional FA supplements and another in New South Wales found it was women with unplanned pregnancies and those living in urban areas (Watson 2006). Two studies from Australia (Williams 2001 and Bower 2005) included data about intake of folate from voluntarily fortified foods (notably breakfast cereals); three studies note a small effect of a FA tablet use intervention and recommend fortification (Egen 2003, Busby 2005, Lawrence 2003), and the remaining three studies do not deal with fortification.

Overall, it appears from these studies that the incidence of NTD has not been reduced as much as it could be through increased periconceptional intake of FA (Busby 2005); many women who are not planning a pregnancy do not take FA supplements, even when they are fully informed about the reasons why they are being asked to do so and are provided with the tablets (Byrne 2003, Lawrence 2003, Chacko 2003); women who do take periconceptional FA supplements are more likely to have higher socio-economic status (Bower 2005, Amitai 2004, Byrne 2003, Egen 2003, Watson 2006); and foods voluntarily fortified with folic acid (primarily breakfast cereals) have been reported (in Australia) to be consumed regardless of socioeconomic status (Bower

2005) and at a household penetration level of over 50% in 1998-9 (Williams 2001). Given that many pregnancies, especially among women of lower socio-economic status, are not planned, it could be that FA fortification strategies merit further consideration, as recommended by Busby (2005) and Egen (2003).

Nutritional interventions (n=2)

Dubois 1997 reported the results of a Canadian retrospective cohort study which used the Higgins Nutrition Intervention Programme to try to reduce adverse pregnancy outcomes and increase birth weight in pregnant adolescents (age <17 y). The intervention group (n=1203, mean week of gestation when intervention began 21.2±7.2 w) was compared to a non-intervention group matched for age, hospital and year (n=1203). The intervention (mean duration = 18 weeks) was an adjunct to routine prenatal care, where each subject's risk profile for adverse pregnancy outcomes was assessed, then an individualised nutritional rehabilitation programme designed by trained dieticians using the Higgins method. The Higgins method was based around 3 risks: under nutrition, underweight and stress conditions – the main aim being to increase protein and energy intake. Additionally, every subject in the intervention group was given a supplement of milk, eggs and vitamins/minerals and, for the poorest, other food. The average recommended increases in daily intake were 900 kcal energy and 52 g protein and the average increases attained were 41% and 44% of those recommendations. The greater the prescribed intake increase the greater the actual increase but no group achieved the prescribed increase. Length of gestation was significantly longer in the intervention group, 39.2±2.1 w versus 39.0±2.6 w, $p \leq 0.05$, and birth weight significantly higher, 55±24 g higher in the intervention group, $p<0.05$.

- The Higgins Nutrition Intervention Programme (mean duration 18 weeks), an individualised nutritional rehabilitation programme including food supplements, was used for Canadian pregnant adolescents (n=1203) (Dubois 1997). Average increases in energy and protein intake were 41% and 44% of those recommended and the greater the recommendation the greater the increase. Length of gestation was significantly longer in the intervention group, 39.2±2.1 w versus 39.0±2.6 w in controls (n=1203), $p \leq 0.05$, and birth weight significantly higher, 55±24 g higher in the intervention group, $p<0.05$.

An American controlled trial of an in-home prenatal nutritional intervention for low-income women primarily aimed to improve dietary intake was reported by Widga 1999. A secondary aim was to identify predictors of low birth weight. The intervention included individualised in-home visits by a nutritionist, weekly for the first 4 weeks, then 2 monthly visits, followed by further monthly visits until the birth (Mean no. of visits = 8±1, range 6-10). Small attainable goals were set from the second session for nutrition and weight gain. Dietary data was obtained initially at ≤24 weeks gestation and after 4 weeks from the Intervention group only (intervention group n=40; control group n=26). There were significant increases in energy, folate, vitamin B6, iron, zinc and calcium intake and in daily servings of vegetables and breads/grains in the intervention group (mostly $p \leq 0.01$) but no comparison was possible with the control group. Infant birthweight was significantly related to mother's weight at delivery, ($p=0.002$) and BMI before pregnancy ($p=0.012$) in the intervention group. There were no significant differences between the intervention and control groups for any outcomes but there was a significant difference in the populations 18% of the intervention group and 42% of the control group were from minority groups.

An American trial (Widga 1999) of an in-home prenatal nutritional intervention for low-income women using goal setting for nutrition and weight gain showed significant increases in energy, folate, vitamin B6, iron, zinc and calcium intake and in daily servings of vegetables and breads/grains in the intervention group (mostly $p \leq 0.01$) but no comparison was made with the control group. The only significant maternal or infant

outcomes found were for infant birthweight and mother's weight at delivery (p=0.002) and BMI before pregnancy (p=0.012) in the intervention group.

References to eleven non-UK, non RCT studies

Amitai Y, Fisher N, Haringman M et al. (2004) Increased awareness, knowledge and utilization of preconceptional folic acid in Israel following a national campaign. *Preventive Medicine: An International Journal Devoted to Practice and Theory* 39 (4): 731-737.

Bower C, Miller M, Payne J et al. (2005) Promotion of folate for the prevention of neural tube defects: who benefits? *Paediatric and Perinatal Epidemiology* 19 (6): 435-44.

Busby A, Armstrong B, Dolk H et al. (2005) Preventing neural tube defects in Europe: A missed opportunity. *Reproductive Toxicology* 20 (3): 393-402.

Byrne J (2003) Folic acid knowledge and use among relatives in Irish families with neural tube defects: an intervention study. *Irish Journal of Medical Science* 172 (3): 118-22.

Chacko MR, Anding R, Kozinetz CA et al. (2003) Neural tube defects: knowledge and preconceptional prevention practices in minority young women. *Pediatrics* 112 (3 Pt 1): 536-42.

Dubois S, Coulombe C, Pencharz P et al. (1997) Ability of the Higgins Nutrition Intervention Program to improve adolescent pregnancy outcome. *Journal of the American Dietetic Association* 97 (8): 871-8.

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.

Lawrence JM, Watkins ML, Ershoff D et al. (2003) Design and evaluation of interventions promoting periconceptional multivitamin use. *American Journal of Preventive Medicine* 25 (1): 17.

Watson LF, Brown SJ and Davey M-A (2006) Use of periconceptional folic acid supplements in Victoria and New South Wales, Australia. *Australian and New Zealand Journal of Public Health* 30 (1): 42-49.

Widga AC and Lewis NM (1999) Defined, in-home, prenatal nutrition intervention for low-income women. *Journal of the American Dietetic Association* 99(9): 1058-62; quiz 1063-4.

Williams P, McHenery J, McMahon A et al. (2001) Impact evaluation of a folate education campaign with and without the use of a health claim. *Australian & New Zealand Journal of Public Health* 25 (5): 396-404.