



Health Development Agency

Prevention of low birth weight:
assessing the effectiveness of smoking
cessation and nutritional interventions

Evidence briefing

July 2003

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Foreword

In 1999 the white paper, *Saving Lives: Our Healthier Nation*, was published. It signalled that the Health Development Agency (HDA) would be established and that it would have, as one of its roles, building the evidence base in public health with a special focus on reducing inequalities in health. In April 2001 the Department of Health published its Research and Development Strategy. The strategy identified the task for the HDA as:

'Maintaining an up-to-date map of the evidence base of public health and health improvement, advising on the setting of standards in the light of evidence, for public health and health promotion practice, and effective and authoritative dissemination of evidence to practitioners.'
(Department of Health, 2001)

In order to translate this into reality the HDA has developed a number of ways of taking a systematic approach to compiling the evidence, identifying gaps and making the evidence base accessible. The publication of this, one in a series of evidence briefings, marks a significant milestone in that activity.

This evidence briefing is a review of reviews about the prevention of low birth weight with an emphasis on smoking cessation and nutrition interventions. The necessity for reviewing reviews, or tertiary level research, stems from the proliferation of systematic and other types of review in medicine and public health over the last decade or more. The HDA has already published evidence briefings on the prevention and reduction of alcohol misuse, teenage pregnancy and parenthood, HIV prevention and health impact assessment. Over the next few months evidence briefings dealing with the following issues will be published: sexually transmitted infections, obesity, smoking, drug use, accidental injuries in children and older people, and depression in older people. Other briefings will be about the promotion of physical activity,

breastfeeding, good mental health, and social support in pregnancy.

Taken together these briefings will provide a comprehensive synthesis of the evidence drawn from systematic and other kinds of reviews. They will all be available on the HDA's website www.hda.nhs.uk/evidence and the electronic versions will be updated on a regular basis as new evidence becomes available.

The first editions of the briefings have been based on evidence drawn from systematic and other kinds of reviews. This means that the type of evidence that does not traditionally find its way into reviews has not been considered in detail for these documents. In future editions of the evidence briefings it is planned to extend the coverage of evidence beyond reviews to other methodologies and other types of study, where these are available.

The construction of the HDA Evidence Base has involved collaboration with a number of partners who have interests and expertise in practical and methodological matters concerning the drawing together of evidence and its dissemination. In particular the HDA would like to acknowledge the following: the NHS Centre for Reviews and Dissemination at the University of York, the EPPI-Centre at the Institute of Education at the University of London, Health Evidence Bulletins Wales, the ESRC UK Centre for Evidence Based Policy and Practice at Queen Mary College, University of London and its nodes at the City University London and the MRC Public Health Sciences Unit at the University of Glasgow, members of the Cochrane and Campbell collaborations, the United Kingdom and Ireland Public Health Evidence Group and the members of the Public Health Evidence Steering Group. This latter organisation acts as the overall guide for the evidence-building project of the HDA. The

cooperation of colleagues in these institutions and organisations has been of significant help in the general work in preparing the framework for how we assess the evidence. The HDA is, however, responsible for the presentation and organisation of the material in the briefings.

We would also like to express our gratitude to the low birth weight evidence base reference group and to HDA colleagues who assisted in organising the literature searches.

Every effort has been made to be as accurate and up to date as possible in the preparation of this briefing. However, we would be very pleased to hear from readers who would like to comment on the content or on any matters relating to the accuracy of the briefing. We will make every effort to correct any matters of fact in subsequent editions. Comments can be made by using our website www.hda.nhs.uk/evidence

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Summary

Introduction

This briefing presents the current evidence from selected good quality systematic reviews/meta-analyses published since 1996. The review will be updated regularly as new evidence becomes available and can be accessed via www.hda.nhs.uk/evidence. It aims to identify smoking cessation and nutrition interventions shown to be effective in preventing low birth weight and is intended to inform policy and decision-makers, NHS providers, public health physicians and other public health practitioners in the widest sense.

Low birth weight is defined by the World Health Organization as a birth weight less than 2,500 grammes (g), since below this value birth weight-specific infant mortality begins to rise rapidly (Kramer, 1987). It is caused by either a short gestation period or retarded intrauterine growth (or a combination of both). Low birth weight is a major cause of infant mortality in developed countries including the UK (Stevens-Simon and Orleans, 1999) and can cast long shadows into adult health status.

In the current UK policy context, there is a renewed emphasis on combating health inequalities at an inter-generational level and, as part of this, giving every child a healthy start in life is a high priority. One of the two headline national targets on health inequality is to reduce the gap in infant mortality between manual groups and the population as a whole by 10% by 2010 (Department of Health, 2002). Babies born weighing less than 2,500g account for around 7% of all live births (7.48% in 1998, England and Wales) (Macfarlane et al., 2000). Low birth weight varies widely according to socio-economic status; for example, between 1991 and 1995, in England and Wales the percentage of low birth weight births was 5.4% in professional social class I (based on the

occupation of the father) compared with 8.2% in unskilled social class V and 9.3% of births registered by the mother alone (Macfarlane et al., 2000).

On the basis of analysis of the literature and with a clear focus on public health and the reduction of inequalities, this briefing focuses on what appears to be the two leading candidates for effective public health intervention in relation to the prevention of low birth weight (Kramer et al., 2000):

- **Interventions to promote smoking cessation**
- **Nutrition interventions among pregnant women.**

Smoking is the major modifiable risk factor contributing to low birth weight. Babies born to women who smoke weigh on average 200g less than babies born to non-smokers. The incidence of low birth weight is twice as high among smokers as non-smokers (Messeccar, 2001). Smoking cessation in pregnancy is strongly affected by socio-economic status, with women of lower education, income and employment status far more likely to continue smoking than women from higher SES groups (Graham and Der, 1999).

The relationship between pregnancy, nutrition and foetal growth has been described as 'deceptively complex' (Osrin and de L. Costello, 2000). However, there is now retrospective and prospective evidence that poor maternal nutritional status at conception and inadequate maternal nutrition during pregnancy can result in low birth weight. A meta-analysis of 277 English and French language studies published between 1970 and 1984 (Kramer, 1987) reported that a number of nutritional factors had an influence on low birth weight, including pre-pregnancy maternal weight, gestational weight gain, energy intake, iron and anaemia.

Methodology

This evidence briefing is a 'review of reviews', that is, a synthesis of high quality systematic reviews, meta-analyses and other syntheses (papers which successfully met the criteria of systematicity, transparency and relevance for the HDA Evidence Base as measured by critical appraisal). Other literature or narrative reviews have informed the context and commentary in this evidence briefing, but have not been accepted for the Evidence Base. The synthesis is not a systematic review of primary data. Furthermore, we have not conducted a systematic search for practice data ('good' or 'best' practice studies) or grey literature. While we believe such data have an important place in the process of gathering evidence to support decisions about effective practice, we currently lack the tools to systematically search and rate such data in an appropriate and sensitive way.

We used the following procedures to identify the reviews to be included in the briefing:

- Systematic searching of the literature
- Selection of relevant systematic reviews and meta-analyses
- Critical appraisal of selected reviews by two readers for transparency, systematicity and relevance
- Assessment of the strength of the evidence, gaps in the evidence identified and recommendations made for further research.

Findings – smoking cessation interventions

Overall effectiveness

- There is systematic review evidence that formal smoking cessation interventions, provided by specialists as part of antenatal care, are effective at increasing smoking cessation rates among pregnant women (Lumley et al., 2001).
- However, larger and more recent trials evaluating smoking in real-life settings, not yet included in the main systematic review on this topic (Dolan-Mullen, 1999; Lumley et al., 2001), indicate less favourable results (Wisborg et al., 1998; Ershoff et al., 2000; Hajek et al., 2001; Moore et al., 2002). The exact content of smoking cessation programmes in pregnancy and how well these transfer from experimental to real-life settings are factors which,

when better understood, are likely to moderate the general findings of effectiveness to emerge from the scientific review-level literature.

Impact of smoking cessation interventions on low birth weight

- There is evidence that effective smoking cessation interventions reduce the prevalence of low birth weight and increase birth weight among pregnant women who quit as a result of intervention (Lumley et al., 2001).

Nicotine replacement therapy (NRT)

- There is insufficient evidence to draw conclusions about the potential benefit or harm resulting from the use of NRT among pregnant smokers (Lumley et al., 2001; Dempsey and Benowitz, 2001).
- The National Institute for Clinical Excellence (NICE) guidance on the use of NRT for smoking cessation recommends NRT 'for smokers who have expressed a desire to quit smoking'. NICE also recommends that 'smokers who are under the age of 18 years, who are pregnant or breastfeeding, should discuss the use of NRT with a relevant healthcare professional before it is prescribed' (NICE, 2002).

Harm reduction

- There is lower quality* review-level evidence to suggest that reducing the number of cigarettes smoked may have a significant impact on low birth weight and health benefits – but this needs to be further investigated in larger trials alongside the development of standardised measures of daily smoking (Windsor et al., 1998; Lumley et al., 2001).

Addressing inequalities

- Despite extensive knowledge about lower rates of cessation and higher rates of low birth weight among lower SES women, review-level evidence does not address the features of effective interventions that might increase smoking cessation in these groups (Dolan-Mullen, 1999; Lumley et al., 2001).

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

Relapse

- High rates of relapse are known to exist among pregnant women who quit smoking. There is a consensus that the transition from pregnancy to the post-partum period is a critical stage for intervention to maintain smoking cessation, yet most interventions are targeted only at the prenatal period. However, there is a lack of review-level evidence about what works to prevent relapse and therefore maintain smoking cessation up to birth and beyond (Dolan-Mullen, 1999; Lumley et al., 2001).

Components of successful interventions

- While there is evidence that smoking cessation interventions in pregnancy are generally effective, less is known about the particular components of interventions which affect outcome. Insights into the way that the effectiveness of interventions can be enhanced or generally implemented are provided in some of the review-level literature, although many of these points need further substantiation. Increasing quit rates through improving the effectiveness of cessation interventions should have a positive effect on low birth weight.
- The review-level literature has little to say about the recruitment of women to cessation programmes. Evidence about effective ways of encouraging participation needs to be gathered.
- Self-help materials should be targeted to the specific audience of pregnant women (Dolan-Mullen, 1999). It is important to note, however, that a recent large randomised controlled trial conducted in the UK (Moore et al., 2002) found that an intervention using self-help booklets targeted at pregnant women was no more effective than normal antenatal care.
- While the review-level evidence suggests that brief interventions are sufficient to produce clinically significant effects and advises against more intensive interventions, this remains a contested area. It is not clear whether more intensive interventions might be appropriate among more heavily addicted smokers who continue to smoke into the last trimester (Dolan-Mullen, 1999; Lumley et al., 2001; Messecar, 2001).
- The pregnant smoker needs to be reached as early as possible and those at most risk of smoking should be carefully targeted, including spontaneous quitters who may have identified themselves as non-smokers, but are vulnerable to relapse. Pre-conception counselling

to encourage cessation before pregnancy is also recommended as a way of bringing forward quit attempts and reducing the likelihood of low birth weight (DiClemente et al., 2000; Messecar, 2001).

- High quality review-level evidence suggests that those involved in implementing interventions need to be trained in order to improve adherence to protocols and maximise effectiveness (Dolan-Mullen, 1999).

Recommendations for research

There remain gaps in knowledge for which new research is needed. Some of these gaps are outlined in the reviews as follows.

- Existing evidence to prevent relapse, both post-partum and during pregnancy, among women who quit needs to be synthesised and disseminated. Relapse prevention may need to be the subject of further primary research (Windsor et al., 1998) before being incorporated into future cessation efforts.
- Having a partner who smokes is one of the critical determinants of pregnant women's smoking behaviour and likelihood of successful quitting. Despite this, cessation efforts directed at, or including, partners of pregnant smokers have received little attention and more research is needed to shed light on how such interventions may improve effectiveness (DiClemente et al., 2000).
- While it seems clear that interventions to promote smoking cessation in pregnancy may be more readily taken up by some groups of women (better educated, higher SES, married) than others, many studies are not yet collecting data which would enable a fuller examination of these trends. More research is needed to establish what type of intervention may increase the effectiveness for lower SES women and their compliance, at what level of intensity and with what added components. The cultural appropriateness of interventions to women from minority ethnic groups also needs more attention in future research.
- More review-level evidence is needed about the effectiveness of interventions when delivered by different medical staff in different settings. Similarly, evidence about encouraging recruitment and participation in cessation programmes is required. Trials also need to report on low birth weight as an outcome, to generally strengthen the evidence.
- The effectiveness of NRT with groups of women who fail to respond to other cessation strategies – such as lower SES women, last trimester smokers, heavily

addicted smokers – and the benefits of NRT for increasing cessation among pregnant women needs to be established in a systematic review.

- While it is known that reaching pregnant women smokers as early as possible is likely to increase the impact on low birth weight, smoking cessation interventions aimed at pre-conception may increase this effect still further. More research is needed to investigate how this may be achieved.
- Successful programmes need to be disseminated and widely adopted. Future evaluation should determine how this might be achieved and what the barriers are to the diffusion and adoption of successful interventions in various care settings.

Findings – nutrition interventions

(See p6 for a summary table of findings)

Calcium supplementation

- There is evidence to support the effectiveness of calcium supplementation for a reduction in preterm birth and the incidence of low birth weight in pregnant women, especially those at risk of hypertensive disorders (Atallah et al., 2001). It is important to note that dietary calcium intakes in the female UK population are low, with 27% of 16-18 year olds and 10% of 19-50 year olds consuming an intake below the Lower Reference Nutrient Intake (400mg a day) (Gregory et al., 1990).

Magnesium supplementation

- There is a lack of evidence to support the routine use of magnesium supplementation during pregnancy to prevent low birth weight (Makrides and Crowther, 2001).

Balanced protein/energy supplementation

- There is conflicting low quality* review-level evidence regarding the effectiveness of balanced protein/energy supplementation in preventing intrauterine growth retardation and small-for-gestational-age (SGA) births.
- There is also low quality review-level evidence that balanced protein/energy supplementation is ineffective

for preventing preterm birth (Kramer, 2001a; de Onis et al., 1998; Villar et al., 1998).

Iso-caloric balanced protein supplementation

- There is low quality review-level evidence that iso-caloric balanced protein supplementation during pregnancy is ineffective for the prevention of SGA and preterm births. This intervention may be harmful (Kramer, 2001b; de Onis et al., 1998; Villar et al., 1998).

High protein supplementation

- There is low quality review-level evidence that high protein supplementation during pregnancy is ineffective for the prevention of low birth weight. This intervention may be harmful (Kramer, 2001c; de Onis et al., 1998; Villar et al., 1998).

Nutritional advice

- There is conflicting evidence from low quality reviews regarding the effectiveness of nutritional advice for the prevention of low birth weight. No conclusions about benefit or harm could be drawn (Kramer, 2001d; de Onis et al., 1998; Villar et al., 1998).

Combined iron and folate supplementation

- There is a lack of review-level evidence regarding the routine use of combined iron and folate supplementation for the prevention of low birth weight. No conclusions about benefit or harm could be drawn (Mahomed, 2001a).

Iron supplementation

- Based on low quality review-level evidence, there is a lack of evidence to support the use of routine iron supplementation for preventing low birth weight (de Onis et al., 1998; Villar et al., 1998).
- In the UK, 6% of women aged 18-24 years, 4% of women aged 25-34 years and 4% of women aged 35-49 years had a low iron status (haemoglobin less than 11.0g/dl) (Gregory et al., 1990). In agreement with Villar et al. (1998) we do not recommend further research within the UK on iron supplementation to prevent low birth weight.

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

Folate supplementation

- There is conflicting low quality review-level evidence regarding the effectiveness of folate supplementation in preventing low birth weight (Mahomed, 2001b; de Onis et al., 1998; Villar et al., 1998).
- In the UK, 4% of women aged 16-50 years have dietary folate intakes below the Lower Reference Nutrient Intake (100 microgrammes (µg) a day) (Gregory et al., 1990). In agreement with Villar et al. (1998) we do not recommend further research within the UK on this topic as a preventive measure for low birth weight.

Zinc supplementation

- There is a lack of review-level evidence to support the use of routine zinc supplementation in pregnant women for the prevention of low birth weight (Mahomed, 2001c; de Onis et al., 1998; Villar et al., 1998).
- The measurement of zinc deficiency within the UK is problematic (Gibson, 1990), and the only available indicator of zinc status is dietary zinc intake. In the UK, 6% of women aged 16-18 years and 4% of women aged 19-50 years have zinc intakes below the Lower Reference Nutrient Intake (4.0 milligrammes (mg) a day) (Gregory et al., 1990). Although some review authors have called for more research, we do not recommend further consideration of zinc supplementation within the UK to prevent low birth weight.

Vitamin D supplementation

- There is conflicting low quality review-level evidence regarding the effectiveness of vitamin D supplementation in preventing low birth weight (de Onis et al., 1998; Mahomed and Gülmezoglu, 2001).

Fish oil supplementation

- There is conflicting low quality review-level evidence regarding the use of fish oil supplementation in the prevention of low birth weight (de Onis et al., 1998; Villar et al., 1998).
- Furthermore, the Department of Health has advised that women should not consume fish oil supplements during pregnancy due to the possibility of high levels of contaminants.

Atypical maternal supplementation (protein free calf blood extract, carnitine, intravenous glucose or oral galactose treatment)

- There is a lack of evidence regarding the effectiveness of atypical maternal nutritional supplementation (protein-free calf blood extract, carnitine, intravenous glucose or oral galactose treatment) in pregnant women with suspected impaired foetal growth. No conclusions about benefit or harm could be drawn (Gülmezoglu and Hofmeyr, 2001).

Recommendations for research

We make the following recommendations for further research, particularly in relation to the general evidence base, the specific nutrients to be studied and trial design.

- We question whether a single intervention is likely to reduce the rate of a multi-causal outcome such as intrauterine growth retardation that is so dependent on socio-economic disparities. Appropriate combinations of interventions should be a priority for evaluation in the context of large methodologically sound trials (de Onis et al., 1998).
- Trials that have been conducted on food-based interventions (rather than nutrient-based), such as the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) or the Expanded Food and Nutrition Education Program (EFNEP) in the USA, should be identified and the suitability of carrying out a systematic review should be assessed.
- The findings also raise questions regarding the appropriate timing and dosage of interventions, considering that long-standing social and nutritional deprivation are difficult to overcome by a nutritional intervention during a few months in the course of a pregnancy. Most trials have been conducted in mid to late pregnancy, which may be too late for nutrient effects to be seen. Foetal growth may, however, be more strongly influenced by a woman's nutritional status around the time of conception. There is an urgent need to understand how maternal nutrition before, and in early pregnancy relates to foetal growth.
- There is an urgent need for more high quality systematic reviews to be written and existing Cochrane reviews to be updated.
- There is a complete lack of systematic review-level evidence regarding the effectiveness of interventions targeting specific socio-economic, ethnic or vulnerable

Review-level evidence on the effectiveness of nutritional interventions for the prevention of low birth weight (LBW)

Evidence of effectiveness	Current lack of evidence of effectiveness	Conflicting evidence of effectiveness	Use not recommended, evidence of potential harm
Calcium supplementation (to reduce preterm birth and LBW, especially those at risk of hypertensive disorders)	Magnesium supplementation (to reduce LBW) Balanced protein/energy supplementation (to reduce preterm birth) Iron and folate supplementation (to prevent LBW) Iron supplementation (to prevent LBW) Zinc supplementation (to prevent LBW) Atypical maternal nutritional supplementation (protein free calf blood extract, carnitine, intravenous glucose or oral galactose treatment) (in pregnant women with impaired foetal growth)	Balanced protein/energy supplementation (to prevent IUGR and SGA births) Nutritional advice in pregnancy (to prevent LBW) Folate supplementation (to prevent LBW) Vitamin D (to prevent LBW) Fish oil supplementation (to prevent LBW)	Iso-caloric balanced protein supplementation (to prevent LBW) High protein supplementation (to prevent LBW)

groups. This is a surprising finding given the higher prevalence of low birth weight among such groups. These groups should be targeted in further research.

- There is no systematic review-level evidence to date regarding the effectiveness of interventions targeting women who have multiple risk factors, eg smoking, poor dietary intake, negative psycho-social factors, etc.
- There is also no reported systematic review-level evidence on the cost effectiveness of nutritional interventions.

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Introduction

The HDA Evidence Base

Decisions about policy and practice in the public sector are increasingly driven by consideration of the best available evidence. The process of drawing together, analysing and synthesising evidence from research is a central principle of evidence-based practice. Typically, the process of reviewing an area of practice or intervention will include the production of a systematic review of effectiveness, a meta-analysis or some other review-level synthesis and interpretation of evidence from research.

As more reviews and meta-analyses are carried out across the spectrum of public health, there is an increasing need to map the areas that they cover, assess their quality and pull together any common findings about what works in particular areas to improve health and reduce health inequalities. The Health Development Agency (HDA) has taken on the task of mapping and synthesising the best available review-level evidence for the effectiveness of interventions to improve health and reduce health inequalities across priority areas of public health. This evidence briefing is part of the first set of publications from the project. Mapping and synthesis of review-level data will enable practitioners and policy-makers to view the aggregate strength of the evidence in key areas, see clearly where review-level evidence is lacking, and inform the development and commissioning of future research and reviews.

Undertaken by the HDA, evidence briefings are essentially reviews of reviews, analysing the strengths and weaknesses at this level in an evidence base of topics, identifying gaps in the evidence, analysing future primary and secondary research needs, and discussing the implications of findings for policy and practice. Each briefing has a freestanding summary that is published separately. The briefings are also published on and

supported by the HDA Evidence Base website (www.hda.nhs.uk/evidence). The website contains the latest edition of this briefing and we recommend that readers refer to the website to ensure they have the latest version. The website also provides access to the original reviews on which these briefings are based, when available. Evidence briefings are designed to be accessed by a variety of users including those simply looking for headline findings, those wanting complete and detailed syntheses, and those who need to track back to the original primary and secondary sources.

Providing comprehensive, up-to-date syntheses of the literature available in reviews is the chosen first step in a process of building the public health evidence base. As our programme of work continues, we will turn our attention to bringing into our evidence briefings work that does not usually find its way into systematic reviews.

Presently, a three-tier structure underpins the HDA's work to develop the public health evidence base:

- 1 A Public Health Evidence Steering Group (PHESG) with membership drawn from universities, public health and research and development divisions of the Department of Health, other government departments, public health practitioners, representatives of research funding bodies, the NHS Centre for Reviews and Dissemination, Cochrane and Campbell Collaborations, the EPPI-Centre, and other UK and WHO representatives. The group is chaired by a high-ranking official from the Department of Health on behalf of the Chief Medical Officer for England. This overarching group advises on the broad strategic direction of the HDA Evidence Base and has a remit to quality assure the processes developed by the HDA to construct the Evidence Base.

- 2 For each topic area covered (eg accidental injuries and low birth weight), there is a reference group. These report to the PHESG, and consist of key academics, practitioners and officials with expertise in the area. Reference groups control the content of the Evidence Base and guide the production of evidence briefings.
- 3 Finally, the HDA is working to establish a robust evaluation framework for the entire Evidence Base project. This will include the formation of user panels to guide and inform our priorities and work.

The next stage in the process is the development of practice advice, derived from the findings of the evidence-based briefings. This evidence-based briefing does not contain advice or guidance for practice. Following publication of this briefing, a similar process of mapping and synthesis, informed and reviewed by practitioner and research experts, will take place leading to practice-based advice and publications.

Who is this briefing for?

It is intended to inform policy and decision-makers, NHS providers, public health physicians and other public health practitioners in the widest sense. Further work will be done to turn the summary of evidence presented here into advice for practice. The limitations of this briefing and the data on which it is based, and alternative sources of evidence that may be helpful to inform policy and practice, are set out below.

What evidence?

At present, the systematic review is probably perceived to be the most robust and reliable marker of effectiveness, closely followed by a well-designed meta-analysis. They are used heavily in clinical sciences to inform practice, and are generally well regarded when used appropriately. This briefing pulls together evidence from systematic reviews of effectiveness, meta-analyses and narrative or literature reviews. Yet relying on this type and level of evidence to inform our conclusions about the prevention of low birth weight has some limitations, and it is important to consider them when making decisions about policy or practice.

Definitions of what constitutes 'good' quality evidence in mainstream public health have been inherited from medical and scientific paradigms, where the experimental

evaluation of clinical efficacy is commonplace and often appropriate. Although there is an increasing use of these approaches, which rely on traditional evidence hierarchies, they may not always be the most appropriate methods of assessing the impact of interventions to improve public health, nor in particular to assess the impact of interventions on health inequalities.

At review (rather than single study) level, meta-analyses and systematic reviews of effectiveness can be very powerful tools for demonstrating the impact (or lack of it) of an intervention. However, they rely heavily on controlled evaluation studies and statistically measurable outcome variables. In contrast, the prevention of low birth weight is highly complex and relational, and almost impossible to capture in terms of quantitative outcomes alone.

A second issue is that, while meta-analyses and systematic reviews (and sometimes, to a lesser extent, literature reviews) are well placed to make judgements about the strength of impact of an intervention, and the quality of the evaluation design, they tend not to examine the appropriateness or quality of an intervention itself, and certainly not in any robust or systematic manner. This can be a source of bias – an inappropriate intervention might have a strong impact on one quantifiable outcome measure, and therefore influence review conclusions, even though that outcome measure might not be the most appropriate or useful. In other words, there is a risk that inappropriate or ill-designed interventions can be given more weight than those that are more suitable (and often more complex or long term), because they may be simpler and quicker to evaluate, or because the interventions can prove some effect relatively easily. However, in spite of these limitations systematic reviews are still a powerful tool in certain circumstances, based as they are on principles of finding good and effective interventions, eliminating harmful interventions, and facilitating public accountability – principles that are important cornerstones to building the HDA Evidence Base.

A third issue is that reviews tend to rely on data from certain types of evaluation design, most often experimental and quasi-experimental trials – thus excluding a substantive amount of literature from their consideration. If this evidence briefing has uncovered no evidence to support a certain intervention or programme, it does not mean there is no evidence out there, just that we have found no evidence included in reviews that meet our criteria.

At present there are problems in trying to incorporate other types of evidence into our evidence briefings. In some areas, such as qualitative research, the thresholds as to what constitutes 'good' quality work are contested by different researchers. There is as yet no agreed method for systematically synthesising or reviewing such work, although there are a number of projects underway nationally and internationally to develop an appropriate methodology. Nor is there any clear or agreed method for combining non-traditional forms of evidence – such as that from qualitative research, action research, expert opinion and so on – with evidence from more traditional types of study to provide a more comprehensive assessment of the effectiveness of different interventions. For the time being, the HDA has taken a first step to pull together evidence from systematic reviews, meta-analyses and good quality narrative reviews, with an acknowledgement that this limits our data pool and may provide only partial answers to our research questions.

A final issue is that of time lag. Inevitably, if one relies on review-level data to gather information about effectiveness, some time – usually one or more years – will elapse between the publication of single studies, the subsequent examination of these single studies by reviewers and the publication of their reviews. Because of the processes involved in carrying out meaningful, high quality research this is to some extent inevitable, and the procedures that cause this delay – the need for publications to be peer-reviewed, the need for a body of work to build up before it can be reviewed and examined – can help avoid publication or positive bias in review findings. It means that the reviews examined by this briefing take into account single studies with a cut-off date of at least one year before the most recent review. If one single study has been published in the meantime that alters common conceptions or consensus about the prevention of low birth weight, it will take a while for the findings of that single study to filter into this forum. We expect to revise and update this briefing, which should ensure that new review data are included swiftly.

In summary, the data presented in this evidence-based briefing – data from reviews – are only a partial answer to 'what works' with respect to the prevention of low birth weight. In using this briefing to inform practice or policy-making, there are a number of other sources of information and evidence that could usefully be taken into account. These include:

- Information from practice studies (eg practice databases, 'best practice' case studies)
- Research studies that are often or usually excluded from systematic reviews and meta-analyses (eg qualitative studies, non-controlled case studies, action research)
- Local data and project evaluations (local to your context and area)
- Expert and practitioner opinion
- Client opinion and experience.

Mapping, collating and making available data from these alternative sources will be a future priority for the HDA. In the meantime, the Public Health Electronic Library (PHeL – www.phel.gov.uk) is a good starting point for the practitioner or policy-maker seeking to take these other types of evidence into account.

What is effectiveness?

In this briefing we use the term to describe demonstrable, intended effects on (usually quantitative) outcomes. However, the term is not uncontested. First, while 'demonstrable' effects, in this context, usually imply those that are statistically significant, in some situations – particularly where interventions require careful, long-term evaluation – this may be an ambitious definition. Secondly, in the UK at least there are some tensions between different kinds of outcome measures, depending on the focus of the study.

The appraisal system that we have used (see the critical appraisal form, Appendix 2) favours reviews that have a transparent and replicable data search, methodology and analysis. This means that systematic reviews of effectiveness and meta-analyses tend to be rated highest (if they are well conducted) because of their clear methodology, relative to literature or other non-systematic reviews. This is not to say that literature reviews cannot be counted as strong evidence – where review rationale, methodology and analytic techniques are clear, they would be rated highly.

A word of caution to include here is that reviews are not always comparing the same thing – some reviews examine outcome data studies, others look at more prospective studies – so interpretation of what we have found is complicated by the state of the data pool. Equally, the reviews themselves sometimes make difficult

or inappropriate comparisons between and across evaluation studies that examine different aspects of the problem.

Summary

This document aims to:

- Identify all relevant systematic reviews, meta-analyses and other reviews
- Review the evidence provided in these papers
- Highlight conflicting evidence and gaps in the evidence, and make recommendations about future research and commissioning.

It does not draw on other sources of evidence, or contain specific advice for practice: this will be developed as part of the next stage of the HDA's evidence into practice work. Systematic review-level evidence is only one source of evidence that should be used to inform guidance for practitioners. Evidence into practice requires gathering evidence from all sources and combining it with political and social information (mindful of resource constraints) to develop learning that will be passed on to practitioners. The HDA has been piloting this process of evidence into practice in two topic areas (physical activity and the prevention of accidental injuries) within the 2002-2003 financial year (Kelly and Speller, 2002).

Background to low birth weight

Low birth weight is defined by the World Health Organization as a birth weight less than 2,500 grammes (g) since below this value birth weight-specific infant mortality begins to rise rapidly (Kramer, 1987). Birth weight is governed by two major processes: duration of gestation and intrauterine growth rate. Low birth weight is thus caused by either a short gestation period or retarded intrauterine growth (or a combination of both). Prematurity is usually defined as a gestational age of less than 37 weeks. Intrauterine growth retardation (IUGR), which is also referred to as small-for-gestational-age (SGA) or small-for-dates, has no generally accepted standard definition, although the following are commonly used (Kramer, 1987):

- Birth weight less than 10th (or 5th) percentile for gestational age
- Birth weight less than 2,500g and gestational age greater than or equal to 37 weeks
- Birth weight less than two standard deviations below the mean value for gestational age.

Though these are often confused in intervention studies, they have distinct aetiological pathways and are amenable to various public health actions.

The relationships between these processes and the outcome of low birth weight are complex; not all preterm births result in low birth weight babies, nor does IUGR directly correlate to birth weight. However, it is true to say that low birth weight is a major cause of infant mortality in developed countries, including the UK (Stevens-Simon and Orleans, 1999). Neonatal death is, however, not the only consequence of low birth weight – it can also cast long shadows into adult health status. Babies born weighing less than 2,500g are also at risk of severe neuro-cognitive and pulmonary morbidity and other long-term health difficulties, including deficits in

growth, cognitive development, diabetes and heart disease (Barker et al., 1990; Barker, 1995). Although birth weight less than 2,500g is a standardised measure of low birth weight and is the definition used in all of the papers which follow, examination of the whole birth weight distribution suggests that birth weight below 3,500g is also sub-optimal for adult health (Barker, 1992).

In the current UK policy context, there is a renewed emphasis on combating health inequalities at an inter-generational level and, as part of this, giving every child a healthy start in life is a high priority. One of the two headline national targets on health inequality is to reduce the gap in infant mortality between manual groups and the population as a whole by 10% by 2010 (Department of Health, 2002a). Furthermore, the Department of Health's *Priorities and Planning Framework 2003-2006* has set targets for reducing health inequalities, including:

'Deliver a one percentage point reduction per year in the proportion of women continuing to smoke throughout pregnancy, focusing especially on smokers from disadvantaged groups as a contribution to the national target to reduce by at least 10% the gap in mortality between "routine and manual" groups and the population as a whole by 2010, starting with children under one year.' (DH, 2002b)

As low birth weight is a leading cause of infant mortality, preventing it is highly important to public health and evidence of effective interventions is urgently needed to contribute to the delivery of these targets.

Prevalence

Babies born weighing less than 2,500g account for around 7% of all live births (7.48% in 1998, England and Wales) (Macfarlane et al., 2000). Many factors affect the prevalence of low birth weight, including the incidence of multiple births – to which recent rises in low birth weight cases have been attributed. Rates of twin births in England and Wales have increased since 1980 from 9.6 per thousand maternities to 13.9 in 1998. Rates of triplet and higher order maternities have also increased dramatically from 0.15 per thousand maternities in 1980 to 0.48 in 1998 (Macfarlane et al., 2000). This is likely to have been affected by the increased use of assisted conception among higher socio-economic status (SES) groups.

Low birth weight varies widely according to socio-economic status in all developed countries, being more prevalent among lower socio-economic groups (Spencer, 2000). This is the case even in countries such as the UK, with free universal antenatal and other healthcare services (Kramer et al., 2000). In the UK there are marked social class differences in rates of low birth weight, with a higher proportion of low birth weight babies born to families where the father is in unskilled or semi-skilled manual work, or among those births registered by the mother alone. For example, between 1991 and 1995 in England and Wales the percentage of low birth weight births was 5.4% in professional social class I (based on the occupation of the father), compared with 8.2% in unskilled social class V, and 9.3% of births registered by the mother alone (Macfarlane et al., 2000).

This social gradient is also paralleled, and often confounded by, marked ethnic differences in low birth weight prevalence. Higher rates of low birth weight are to be found among black women in the USA and Asian women in the UK (Kramer et al., 2000). This pattern is not to be found in all ethnic groups, even among those that share certain aspects of social disadvantage. Mexican immigrant women in the USA, American Indian groups in Canada and North African immigrant women in Israel, for example, are less likely to have low birth weight babies than other groups (Kramer, 1998). International comparisons suggest that factors beyond genetic constraints are responsible for differences in birth weight within populations and that birth weight distributions can potentially be altered by public health interventions (Paneth, 1995).

Determinants

The main risk factors or potential mediating variables between low socio-economic status and low birth weight are reviewed by Kramer et al. (2000), adapted and summarised as follows.

Risk factor	Link with low SES
Anthropometry/nutritional status	Short stature, low pre-pregnancy body mass index (BMI), low gestational weight gain more common in low SES women
Micronutrients	Low dietary intake more common in low SES women
Cigarette smoking	Higher prevalence and heavier smoking among low SES women
Substance misuse	More common among low SES women
Work/physical activity	Prolonged standing and strenuous work more common among low SES women
Prenatal care women	Lower uptake among low SES
Bacterial vaginosis	More common in low SES women
Multiple birth	Less common among lower SES groups
Psycho-social factors	More stressful life events, more chronic stressors, more common depression and low levels of social support in low SES groups

Kramer et al. (2000) provide an analysis of the evidence relating to each of the above causal factors to assess the contribution of each to the overall social gradient in low birth weight. They concluded that:

'Cigarette smoking during pregnancy appears to be the most important mediating factor for IUGR, with low gestational weight gain and short stature also playing substantial roles. For preterm birth, socio-economic gradients in bacterial vaginosis and cigarette smoking appear to explain some of the socio-economic disparities.'

A recent review of risk factors in the form of a meta-analysis (Shah and Bracken, 2000) provides strong support for the role of cigarette smoking as a causal factor in preterm delivery, with greater risk associated with heavier smoking.

Although clearer (if as yet incomplete) knowledge is emerging about the causal pathways between low social status and birth weight, there is much less evidence on effective preventive interventions. Some of the areas which may appear amenable to public health action in combating low birth weight have had disappointing results.

For example, the hypothesis that more deprived women suffer greater stresses and that this may predispose them to preterm delivery is well developed at a theoretical level (Hoffman and Hatch, 1996). However, there is little evidence from reviews to suggest that social support interventions had any demonstrable effect on low birth weight as a birth outcome (Hodnett, 2001). Increasing the coverage, availability or quantity of prenatal care services also appears, particularly in the US context, to have had little impact on low birth weight prevalence (Wynn and Wynn, 1997). This is not to deny, however, the important impact that aspects of routine antenatal care may have upon mediating variables such as smoking rates (Bergsjö and Villar, 1997).

This paucity of evidence from intervention studies has led commentators to suggest low birth weight is an apparently intractable problem, or to try and find explanations within study methodology for the 'enigma of failure' surrounding interventions to prevent it (Stevens-Simon and Orleans, 1999).

Scope of this evidence briefing

On the basis of analysis of the literature and with a clear focus on public health and the reduction of inequalities, this briefing focuses on what appears to be the two leading candidates for effective public health intervention in relation to the prevention of low birth weight (Kramer et al., 2000):

- **Interventions to promote smoking cessation among pregnant women**
- **Nutrition interventions among pregnant women.**

This focus is not intended to oversimplify the complex factors implicated in low birth weight; rather, it is to highlight interventions which more clearly fall within the sphere of public health (as opposed to healthcare/treatment), and bring together review-level evidence about interventions likely to yield the greatest positive impact.

This briefing does not assess the effectiveness of healthcare interventions to treat low birth weight infants as this work is beyond a public health remit.

It should be noted that only a relatively small subset of trials within the review-level evidence have reported on low birth weight as an outcome measure. However, these establish a link between smoking cessation and improvement in low birth weight. Since the review-level evidence examined here is of smoking cessation and nutritional studies, the potential link to low birth weight is sometimes implicit. Where the review data make the link in a more explicit way, this is reported.

The evidence assessed was restricted to that provided by high quality* systematic reviews or meta-analyses. Other

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

literature or narrative reviews have informed the context and commentary in this briefing, but have not been accepted for the HDA Evidence Base. These are listed under 'Other material'. Where the interpretation and conclusions of the review-level evidence were not in agreement or were contradictory, these findings have been described as conflicting.

This report is a 'review of reviews', that is, a synthesis of systematic reviews, meta-analyses and other syntheses, known as secondary data sources, as they have collated and interpreted original studies (primary data), and provided an interpretive overview of the collated findings. The primary data were typically derived from randomised controlled trials (RCTs); however, where there was a lack of RCT research, findings were elicited from other studies such as non-RCT, quasi-experimental or observation studies. This synthesis is not a systematic review of primary data. We have not conducted a systematic search for practice data ('good' or 'best' practice studies) or grey literature. Again, this is not to discount the validity of such data – we believe they have an important place in the process of gathering evidence for making decisions about effective practice. However, tools enabling such data to be systematically searched and rated in an appropriate and sensitive way are yet to be fully developed.

Search strategy

An extensive and systematic search of the literature was conducted. The search strategy was devised in collaboration with the NHS Centre for Reviews and Dissemination, University of York. There were two separate search strategies for smoking and nutrition-based interventions in relation to prevention of low birth weight (see Appendix 1 for examples). Searches were conducted on the following electronic databases:

- Cochrane Library
- DARE database (further details available from <http://agatha.york.ac.uk/faq2.htm>)
- 'Wider Public Health' report
- MEDLINE
- TRIP
- Health Technology Assessment Database
- Health Evidence Bulletins Wales
- National Guidelines Clearinghouse
- National Coordinating Centre for Health Technology Assessment
- National Institute of Clinical Evidence (NICE) website
- REFER
- National Research Register
- Clinical Evidence
- EMBASE
- Sociological abstracts
- PsycINFO
- EPPI-Centre, Institute of Education, University of London
- DH website
- Psychological abstracts
- Campbell
- PsycLit
- CINAHL
- SOCIOFILE
- Social science citation index

All databases were searched from January 1996 to October 2001. All 270 citations were downloaded onto Reference Manager software.

Data handling process

Titles and abstracts of identified references were independently assessed for relevance by two authors. The following inclusion criteria were used:

- English language only
- January 1996 to October 2001
- Human studies
- Systematic reviews, syntheses and meta-analyses
- Interventions relating to smoking cessation in pregnancy
- Nutrition interventions to prevent low birth weight, IUGR (SGA), or preterm birth.

Where no clear decision could be made on the basis of the title or abstract, studies were considered relevant.

Reference lists of all 76 relevant papers were also searched to identify further papers.

All papers were assessed independently by two authors and critically appraised in terms of transparency, systematicity and relevance according to HDA Evidence Base methodology (Kelly et al., 2002). There was no blinding of authorship of retrieved papers. Any queries regarding the methodology of the review or meta-analysis were followed up with the authors. A critical appraisal form was completed by each reviewer (Appendix 2) and a joint decision made regarding whether the paper was suitable for the HDA Evidence Base (ie papers which successfully met the criteria of systematicity, transparency and relevance for the HDA Evidence Base as measured in the critical appraisal form), whether it could be used to inform discussion, or discarded. Disagreements were resolved through discussion or if necessary, by recourse to a third reviewer.

The HDA Evidence Base papers were compared and findings collated. Conflicting evidence was identified and gaps in the evidence charted. Within each section, we make a number of summary statements about whether certain interventions were effective, based on the evidence from the included HDA Evidence Base papers.

Smoking and low birth weight

Smoking is the major modifiable risk factor contributing to low birth weight. Babies born to women who smoke weigh on average 200g less than babies born to non-smokers. The incidence of low birth weight is twice as high among smokers as non-smokers (Messecar, 2001). Smoking is the most important causal factor mediating low SES and IUGR (Kramer et al., 2000), but also has an established causal role in preterm delivery (Shah and Bracken, 2000), though this is perhaps less significant. In both cases there is evidence of a dose-response relationship, with a progressively higher incidence of low birth weight among heavier smokers (Shah and Bracken, 2000; Messecar, 2001). The DH's *Tackling Health Inequalities* report (DH, 2002c) states that if no mothers smoked the average birth weight would rise by an estimated 36g. Smoking cessation efforts for pregnant women therefore represent a major opportunity for public health intervention in reducing the prevalence of low birth weight and its knock-on contribution to infant mortality and morbidity.

Pregnancy is a critical transition in women's smoking careers, acting as a trigger to spontaneous cessation for a large number of women. It is estimated that around 80-85% of these women are able to maintain smoking cessation throughout their pregnancy but that over 70% return to smoking within six months of the birth of the baby (DiClemente et al., 2000). Studies of relapse prevention in pregnancy have so far shown disappointing results (Van't Hof et al., 2000).

Smoking cessation in pregnancy is highly differentiated by socio-economic status, with women of lower education, income and employment status far more likely to continue smoking than women from higher SES groups (Graham and Der, 1999). Smoking in pregnancy is four times more prevalent among women in household social class V than those in social class I. Teenage mothers are the most likely of all age groups to smoke in

pregnancy – nearly two thirds of under 20s smoke before pregnancy and almost a half during it (DH, 2002c). King et al. (1997) also suggest that women from minority ethnic groups face particular barriers to quitting including poverty, psychological ill-health, cultural health beliefs and language difficulties. They go on to note the paucity of current interventions targeted to such women.

Despite high rates of post-partum relapse, pregnancy doubtless represents 'unrivalled opportunities for cessation' (Graham and Der, 1999). It is currently recommended that pregnant women smokers receive specialist support with smoking cessation in the antenatal period (West et al., 2000). What sort of support, from whom and how, are issues to which review-level evidence provides only some of the answers.

Findings

The findings have been drawn primarily from two reviews (listed below), which have been accepted onto the HDA Evidence Base (the review by Dolan-Mullen, 1999, is an update of Dolan-Mullen et al., 1994).

HDA Evidence Base papers

Dolan-Mullen, P. (1999). Maternal smoking during pregnancy and evidence based interventions to promote cessation. *Primary Care* 26: 577-89.

Dolan-Mullen, P., Ramirez, G. and Groff, J. Y. (1994). A meta-analysis of randomised trials of prenatal smoking cessation interventions. *American Journal of Obstetrics and Gynecology* 171: 1328-34.

Lumley, J., Oliver, S. and Waters, E. (2001). Interventions for promoting smoking cessation during pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Other material

Other literature or narrative reviews have informed the context and commentary in this briefing and are listed below. However, these papers have not met the systematicity, transparency and relevance criteria for the HDA Evidence Base.

Supplementary papers

Dempsey, D. and Benowitz, N. (2001). Risks and benefits of nicotine to aid smoking cessation in pregnancy. *Drug Safety* 24: 277-322.

DiClemente, C., Dolan-Mullen, P. and Windsor, R. (2000). The process of pregnancy smoking cessation: implications for interventions. *Tobacco Control* (Suppl III): iii16-iii21.

Hajek, P., West, R., Lee, A., Foulds, J., Owen, L., Eiser, R. and Main, N. (2001). Randomised controlled trial of a midwife-delivered brief smoking cessation intervention in pregnancy. *Addiction* 96: 485-94.

King, T., Borrelli, B., Black, C., Pinot, M. P. and Marcus, B. H. (1997). Minority women and tobacco; implications for smoking cessation interventions. *Annals of Behavioural Medicine* 19: 301-10.

McNeill, A., Foulds, J. and Bates, C. (2001). Regulation of nicotine replacement therapies (NRT): a critique of current practice. *Addiction* 96: 1757-68.

Melvin, C. L., Dolan-Mullen, P., Windsor, R. A., Pennington Whiteside Jr, H. and Goldenberg, R. L. (2000). Recommended cessation counselling for pregnant women who smoke: a review of the evidence. *Tobacco Control* 9 (Suppl III): 80-4.

Messecar, D. (2001). Smoking cessation interventions for pregnant women: what does the evidence show? *Journal of Academy of Nurse Practitioners* 3: 171-7.

Silagy, C., Mant, D., Fowler, G. and Lancaster, T. (1997). The effect of nicotine replacement therapy on smoking cessation (Cochrane Review). In: *The Cochrane Library*, Issue 2. Update Software: Oxford.

Windsor, R., Boyd, N. R. and Orleans, T. (1998). A meta-evaluation of smoking cessation intervention research among pregnant women: improving the science and the art. *Health Education Research* 13: 419-38.

Wisborg, K., Henriksen, T. B. and Secher, N. J. (1998). A prospective intervention study of stopping smoking in pregnancy in a routine antenatal care setting. *British Journal of Obstetrics and Gynaecology* 105: 1171-6.

Characteristics of the trials included in the review-level evidence are shown in Table 1. The majority of studies included were conducted in developed countries in hospital or antenatal care settings. There was a range in quality between review papers and only two systematic reviews fulfilled the quality criteria for the HDA Evidence Base.

Overall effectiveness

Overall effectiveness of smoking cessation interventions has been found in review-level data. Lumley et al. (2001), in the only systematic review on this subject, revealed a significant reduction in the odds of continued smoking in late pregnancy in the groups receiving intervention in an antenatal care setting (odds ratio (OR) 0.53, 95% confidence interval (CI): 0.47-0.60). Levels of effectiveness varied slightly when analysis was restricted to subsets of trials of high methodological quality, of higher intensity, and with bio-chemically validated smoking cessation, but remained statistically significant. The summary findings of the systematic review are that 'of 100 women still smoking at the time of recruitment typically about 10 will stop smoking with usual care and a further six or seven will stop as a result of a formal smoking cessation programme' (Lumley et al., 2001).

Dolan-Mullen et al. (1994, 1999) in a meta-analysis and subsequent update of trials of various interventions conducted between the sixth and ninth month of pregnancy, calculated a combined risk ratio for smoking cessation after intervention and also found that smoking cessation interventions were effective in increasing cessation in pregnancy. In interpreting risk ratios of 1.5 (95% CI: 1.61-2.34) in the original meta-analysis and 1.7 (95% CI: 1.26-2.25) in the more recent update, this study concludes that intervention can increase smoking cessation by up to 70%, though the degree of effectiveness varies among trials and within different subgroups of women. There was significant heterogeneity in treatment effects across individual studies and inclusion criteria were not described, so these results should be treated with caution.

Data from Dolan-Mullen's meta-analysis (1999) had been used to inform the recommended cessation guidelines for pregnant women who smoke, produced by an expert consensus panel in the USA (Melvin et al., 2000). This panel concluded that brief cessation counselling of five to 15 minutes, when delivered by a trained provider and accompanied by pregnancy specific training materials,

Table 1: Characteristics of the review-level evidence of smoking cessation interventions to prevent low birth weight

Author and year	Number and type of studies included	Setting	Participants	Protocol
Dolan-Mullen (1999)	16 randomised controlled trials with validated smoking outcomes	Public, hospital and university clinics. Health management organisations and WIC sites. Trials conducted in the USA, Canada, Australia, Sweden	6,519 women from diverse socio-economic levels and ethnic and racial groups	13 trials provided counselling of varying duration. Most of the trials used counsellors who were trained and supervised by the investigators. Booklets, pamphlets, self-help manuals, audio and video tape were also used. All studies used materials specifically directed for a pregnancy audience. Cessation was measured between the sixth and ninth month of pregnancy
Lumley et al. (2001)	44 randomised or quasi-randomised controlled trials. Pooled odds ratios were based on 34 trials. Databases were searched for trials between 1975 and 1998	Subjects recruited via antenatal care (hospitals and community clinics) in USA, Canada, Argentina, Brazil, Cuba, Mexico, Australia, UK, Norway, Sweden	Over 17,000 healthy smoking pregnant women recruited before 28 weeks gestation	Diverse strategies including counselling, health education, relapse prevention, booklets, pamphlets and other self-help materials. Continued smoking in late pregnancy was the main outcome measure
Melvin et al. (2000)	<i>The evidence in this review is the same as in Dolan-Mullen (1999)</i>			
Messecar (2001)	Five controlled trials. All trials included measurement of outcome LBW in addition to smoking cessation rates	Public clinics and health management organisations in the USA and Sweden	2,266 women. One trial had one of the highest percentages of African-American participation in any study	Counselling provided by trained counsellors, self-help manual and literature targeted for pregnant women. All studies measured smoking status by salivary or blood thiocyanate, cotinine validation or exhaled carbon monoxide
Windsor et al. (1998)	23 experimental or quasi-experimental studies. Databases were searched for trials between 1986 and 1998	Public, hospital and university clinics. Health management organisations and WIC sites. Trials in the USA, Canada, UK, Australia, Norway, Sweden	13,854 women recruited before 28th week gestation	Diverse strategies including counselling, health education, relapse prevention, booklets, pamphlets and other self-help materials. Validated smoking outcome measurements collected in 15 studies using saliva and urine cotinine, salivary thiocyanate or exhaled carbon monoxide

■ = HDA Evidence Base papers

increased rates of cessation among pregnant women in line with the 70% identified by Dolan-Mullen (1999).

Interventions involving additional group sessions during pregnancy were reported in Lumley et al. (2001) as being poorly attended and therefore ineffective in all trials.

Based on the evidence from the included HDA Evidence Base papers: there is evidence that formal smoking cessation interventions, provided by specialists as part of antenatal care, are effective at increasing smoking cessation rates among pregnant women.

By way of caution, it is worth noting that larger and more recent trials evaluating smoking in real-life settings (without specially employed staff to carry out the intervention), not yet included in the main systematic reviews on this topic (Dolan-Mullen, 1999; Lumley et al., 2001), indicate less favourable results (Wisborg et al., 1998; Ershoff et al., 2000; Hajek et al., 2001; Moore et al., 2002). The exact content of smoking cessation programmes in pregnancy and how well these transfer from experimental to real-life settings are factors which, when better understood, are likely to moderate the general finding of effectiveness to emerge from the review-level literature.

Impact of smoking cessation interventions on low birth weight

Lumley et al. (2001) analysed a subset of trials which included information on low birth weight and found a reduction in low birth weight among intervention groups (pooled odds ratio 0.80, 95% CI: 0.67-0.95) and an overall increase in mean birth weight of 29g (although this weight increase may not confer health benefits). Dolan-Mullen's meta-analysis (1999) also shows a small reduction in low birth weight but on the basis of only two studies. Lumley et al. (2001) highlight the significance of even small reductions in low birth weight given the lack of evidence of other interventions likely to impact on this outcome.

Based on the evidence from the included HDA Evidence Base papers: there is evidence that effective smoking cessation interventions reduce the prevalence of low birth weight and increase birth weight among pregnant women who quit as a result of intervention. More trials need to report on low birth weight as an outcome of intervention to enhance the strength of this evidence.

Nicotine replacement therapy (NRT)

There is evidence of effectiveness of NRT in the general population of smokers (Silagy et al., 1997). The National Institute for Clinical Excellence (NICE) guidance on the use of NRT for smoking cessation recommends NRT 'for smokers who have expressed a desire to quit smoking'. However, NICE also recommends that 'smokers who are under the age of 18 years, who are pregnant or breastfeeding should discuss the use of NRT with a relevant healthcare professional before it is prescribed' (NICE, 2002). The use of NRT in pregnancy might be recommended for those who fail to respond to psychosocial interventions (Melvin et al., 2000). A growing body of opinion (McNeill et al., 2001) also suggests that the benefits of NRT are likely to far outweigh any potential harm in comparison to continued smoking during pregnancy. However, there is currently insufficient review-level evidence to establish firmly the efficacy and safety of this treatment during pregnancy (Lumley et al., 2001; Dempsey and Benowitz, 2001). A systematic review of the existing trial evidence is needed to establish the benefits of this strategy for increasing cessation among pregnant women who are more heavily addicted smokers.

There is insufficient evidence to draw conclusions about the potential benefit or harm resulting from the use of NRT among pregnant smokers.

Harm reduction

While the evidence reported here has focused on cessation as the main outcome of intervention, some authors note that reducing the number of cigarettes smoked is another important outcome of intervention with potentially significant health benefits in terms of low birth weight. Windsor et al. (1998) report on four studies which developed validated measures of smoking reduction. Women who reduced their smoking exposure levels by 50% or more, based on analysis of saliva cotinine, had babies whose birth weights were on average 92g heavier than the group who did not change their smoking behaviour. Quitters had infants whose birth weights were on average 250g heavier than those who continued smoking at their baseline rate (on an individual and population basis, this weight increase will confer health benefits). Such findings need to be further replicated in large trials. Lumley et al. (2001) concluded that questions remain about the effectiveness of interventions to facilitate smoking reduction, but that measures should be developed to reliably assess the amount of daily smoking in future trials.

There is lower quality* review-level evidence to suggest that reduction in smoking may have a significant impact on low birth weight and health benefits – but this needs to be further investigated and standardised measures need to be developed.

Addressing inequalities

It is widely acknowledged in the literature on smoking and pregnancy that quit rates among pregnant women are highly differentiated by socio-economic status. Lumley et al. (2001) did not indicate how the effectiveness demonstrated by interventions included in their review might be distributed among different social groups. However, the authors noted that attrition rates from trials were higher among women who were poor, in receipt of means-tested benefits and who were more likely to move. Dolan-Mullen (1999) noted the differences

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

in cessation rates among women of lower SES (4-20% in low income groups compared with 16-26% in higher income groups), though the differences were in absolute levels of cessation, with relative improvement being similar among both groups. Melvin et al. (2000) found that brief counselling and self-help materials as recommended by an expert panel were at least as effective with women from minority ethnic groups as with white, non-Hispanic women, based on evidence from two trials.

Dolan-Mullen (1999) suggested that as lower SES women report more stressful life events and lower levels of social support, more intensive interventions with additional social support components were needed for this group, but this was an untested hypothesis.

Despite extensive knowledge about lower rates of cessation and higher rates of low birth weight among lower SES women, review-level evidence does not describe the features of effective interventions to increase smoking cessation in these groups.

Relapse

High rates of relapse are known to exist among pregnant women who quit smoking. Dolan-Mullen (1999) estimated that up to 75% of women who stopped smoking during pregnancy returned to the habit within six months of delivery and half did so in the first six weeks after giving birth. Relapse can also occur before the birth among those who are spontaneous quitters. Lumley et al. (2001) and Dolan-Mullen (1999) estimate that around 25% of quitters resume smoking within the period of the pregnancy. Data from one trial in the review of Lumley et al. (2001) suggest that the transtheoretical model of stages of change in readiness to stop smoking may be different in pregnant women, with state changes not sustained beyond early pregnancy.

There is a consensus that the transition from pregnancy to the post-partum period is a critical stage for intervention to maintain smoking cessation. However, most cessation programmes are targeted only at the prenatal period. On the basis of five trials, Dolan-Mullen (1999) suggests that relapse prevention should be a targeted component of interventions, but comments that this may not increase maintenance significantly.

As cessation during pregnancy is clearly more critical for preventing low birth weight, evidence regarding relapse prevention is needed for women who quit but are vulnerable to relapse.

There is a lack of review-level evidence about what works to prevent relapse and therefore maintain smoking cessation up to birth and beyond.

Components of successful interventions

While there is review-level evidence of the overall effectiveness of smoking cessation interventions in pregnancy, less is known about the effects of particular components of interventions. We need to know more about factors such as recruitment and targeting in order to increase the effectiveness of interventions which will in turn impact on low birth weight.

Recruitment

The review-level literature has little to say about the recruitment of women to cessation programmes. Evidence about effective ways of encouraging participation in such interventions needs to be gathered.

Targeting of materials

Dolan-Mullen (1999) stressed the importance of targeting self-help materials to the specific audience of pregnant women. This was based on evidence from one early trial in her study where general smoking cessation materials were provided and treatment effects were half that of trials providing self-help materials specifically targeted for pregnant women. The cultural transferability and 'acceptability' of such materials to different groups of women (such as those for whom English is not a first language or those with low levels of literacy) in different contexts was an important consideration (King et al., 1997).

Intensity

While more contact in interventions has been shown to increase effectiveness in the general population of smokers, Dolan-Mullen's (1999) study observes that no such dose-response relationship is observed among pregnant women. Similarly, Lumley et al. (2001) found only a small increase in effect size among trials in a subset of more intensive interventions. Based on this review-level evidence, the US experts have concluded that 'more intensive counselling has not been documented to increase cessation rates among pregnant smokers' (Melvin et al., 2000).

Contrary to this finding, lower quality* review-level evidence asserts that 'more intensive intervention with multiple contacts produced larger effects' (Messecar, 2001).

So, while the review-level evidence suggests that brief interventions are sufficient to produce clinically significant effects and advises against the design of more intensive interventions, this remains a contested area. It is not clear whether more intensive interventions might be appropriate among more heavily addicted smokers who continue to smoke into the last trimester.

Timing

Based on one trial, Messecar (2001) in a non-systematic review of evidence suggested that early quitting resulted in a greater reduction in the odds ratio for low birth weight than quitting after the first trimester. The author also suggested that this indicated that cessation efforts should be focused on women's early contacts with the healthcare system. DiClemente et al. (2000) echoed the importance of reaching the pregnant smoker as early as possible, emphasising the need for careful targeting of smoking risk, including those spontaneous quitters who may have identified themselves as non-smokers, but are vulnerable to relapse. Pre-conception counselling to encourage cessation before pregnancy was also recommended as a way of bringing forward quit attempts and reducing the likelihood of low birth weight. This should not detract from the need to design and deliver interventions throughout pregnancy to continue to encourage quitting and prevent relapse.

Training

High quality* review-level evidence suggested that those involved in implementing interventions need to be trained in order to improve adherence to protocols and maximise effectiveness (Dolan-Mullen, 1999). However, more review-level evidence is needed about the effectiveness of interventions when delivered by different medical staff in different settings.

There is high quality* review-level evidence about some components of smoking cessation interventions that enhance effectiveness, such as targeting of materials, appropriate intensity of interventions and training.

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

It is important to note, however, that a recent large randomised controlled trial conducted in the UK (Moore et al., 2002) found that an intervention using self-help booklets targeted to pregnant women was no more effective than normal antenatal care.

The strength of the evidence

The high quality review-level evidence drawn on in this briefing comes from one systematic review and one meta-analysis, the latter with some methodological weaknesses. Other lower quality review-level evidence from narrative reviews or expert consensus provides weaker evidence overall. Although the case for the overall effectiveness of smoking cessation is well established and the links between cessation and improvement in low birth weight are promising, the evidence relating particular types or components of interventions with degrees of effectiveness is weaker.

In addition, authors of reviews note several methodological weaknesses in the primary studies which limit the strength and generalisability of the evidence (Lumley et al., 2001; Windsor et al., 1998). They make the following recommendations for improvements to future trials:

- Trials should include data on low birth weight and other pregnancy outcomes as well as cessation outcomes
- Fuller descriptions of interventions should be provided to include content, theoretical basis, intensity, training for providers and cost data
- Method of randomisation and concealment of allocation should be fully reported
- Process data should be collected and reported including data on patient recruitment and compliance, and the perceptions of women participating in interventions. This will improve our understanding of how interventions achieve their results and which factors are likely to enhance success
- Demographic characteristics of patients should be recorded and analysed with sample sizes sufficiently large for subgroup analysis
- Biochemical validation of smoking status (by salivary or blood thiocyanate, cotinine validation or exhaled carbon monoxide) should be included to improve internal validity and to measure significant reductions in smoking

- Measures of continued smoking abstinence are required instead of point prevalence (one off measurement).

Gaps in the evidence and recommendations for research

While improving the methodological quality of trials as recommended above will go some way to strengthening the evidence base in this area, there remain gaps in knowledge for which new research is needed.

- Findings from existing intervention research to prevent relapse, both post-partum and during pregnancy, among women who quit need to be synthesised and disseminated. It is suggested that relapse prevention may need to be the subject of further primary research (Windsor et al., 1998) before being incorporated into future cessation efforts.
- Having a partner who smokes is one of the critical determinants of pregnant women's smoking behaviour and likelihood of successful quitting. Despite this, cessation efforts directed at, or including, partners of pregnant smokers have received little attention and more research is needed to shed light on how such interventions may improve effectiveness (DiClemente et al., 2000).
- While it seems clear that interventions to promote smoking cessation in pregnancy may be more readily taken up by some groups of women (ie better educated, higher SES, married) than others, many studies are not yet collecting data which would enable a fuller examination of these trends. More research is needed to establish what type of intervention may increase the effectiveness for lower SES women and their compliance, at what level of intensity and with what added components. The cultural appropriateness of interventions to women from minority ethnic groups also needs more attention in future research.
- The effectiveness of NRT with groups of women who fail to respond to other cessation strategies – such as lower SES women, last trimester smokers, heavily addicted smokers – and the benefits of NRT for increasing cessation among pregnant women need to be established in a systematic review.
- More review-level evidence is needed about the effectiveness of interventions when delivered by different medical staff in different settings. Similarly, more needs to be known about encouraging recruitment and participation in cessation programmes. Trials also need to report on low birth weight as an outcome, to generally strengthen the evidence.
- Reaching pregnant women smokers as early as possible is likely to increase the impact on low birth weight, and smoking cessation interventions aimed at pre-conception may have even more effect. More research is needed to investigate how this may be achieved.
- Successful programmes need to be disseminated and widely adopted. Future evaluation should determine how this might be achieved and what the barriers are to the diffusion and adoption of successful interventions in various care settings.

Nutrition and low birth weight

Background (see also 'Background to low birth weight', p12)

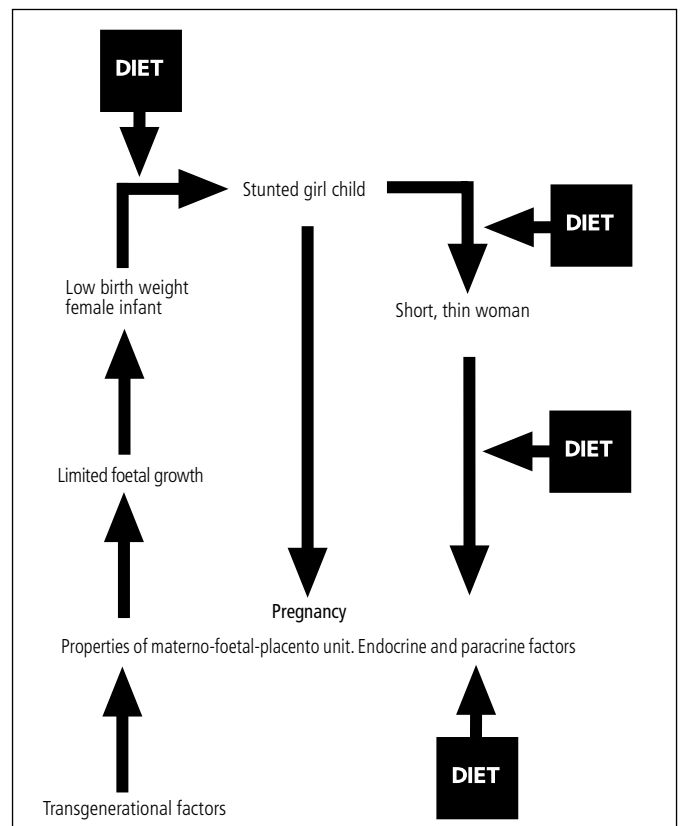
The relationship between pregnancy, nutrition and foetal growth has been described as 'deceptively complex' (Osrin and de L. Costello, 2000). However, there is now retrospective and prospective evidence that poor maternal nutritional status at conception and inadequate maternal nutrition during pregnancy can result in low birth weight. A meta-analysis of 277 English and French language studies published between 1970 and 1984 (Kramer, 1987) reported that a number of nutritional factors had an influence on low birth weight:

- Pre-pregnancy maternal weight is the strongest predictor of infant weight (Osrin and de L. Costello, 2000) and reflects nutritional stores potentially available to the growing foetus. In women with a pre-pregnancy weight of less than 49.5 kilogrammes (kg), there is an 84% increase in risk of IUGR and a 25% increase in risk of preterm birth
- Gestational weight gain. Maternal energy intake and nutritional stores are the sole source for foetal energy requirements, therefore weight gain during pregnancy has been shown to affect IUGR. There is a 98% increase in risk of IUGR in women with low gestational weight gain (less than 7kg)
- Energy intake is closely related to gestational weight gain and was found to influence birth weight
- Iron and anaemia. An association between maternal haemoglobin concentration and IUGR and preterm birth has been reported. Maternal anaemia during early pregnancy was associated with a 32% increased risk of preterm birth and a non-statistically significant 39% increased risk of low birth weight (Xiong et al., 2000).

Kramer (1987) recommended public health interventions that were likely to have a short-term impact on

intrauterine growth in developed countries, including improved pre-pregnancy weight and maternal caloric intake, especially where nutrition was suboptimal for a substantial minority of the population. An update of Kramer (1987) confirmed these findings and concluded that 'although the available evidence does not support an aetiological role for micronutrients in either IUGR or preterm birth, there is ample room for large trials in populations with low dietary or vitamin supplementary intakes, and for observational studies of genetic, lifestyle or other nutritional factors that may increase the effects of (ie interact with) low intakes' (Kramer et al., 2000).

Figure 1: The cyclical nature of the influences on foetal growth (source: Osrin and de L. Costello, 2000)



It has also been suggested that nutrition in women should now be approached in terms of life cycles (Osrin and de L. Costello, 2000), as shown in Figure 1.

Dietary changes at four different stages could affect birth weight. Many other factors may also exert an influence at these stages. An important consideration is whether nutrition sets a pattern within women that limits the potential growth of their babies, which in turn may have long-term consequences, and at what point this pattern is established.

Within the current UK policy context there is a renewed emphasis on combating health inequalities, which includes rates of low birth weight babies. The findings of the independent inquiry into inequalities in health states that 'a baby's health is related to the nutrition and physique of its mother' and recommends 'policies which improve the health and nutrition of women of childbearing age and their children, with priority given to the elimination of food poverty' (Acheson, 1998). However, it has been suggested that 'socio-economic disadvantage is probably not a direct, independent determinant of foetal growth and that socio-economic disadvantage may lead to adverse psychological, behavioural or other environmental exposures that restrict foetal growth' (Kramer, 1998).

This evidence briefing describes interventions that work to prevent low birth weight (IUGR and preterm birth). Policy-makers should use this information in conjunction with other sources of information from health, society and politics to determine a course of action to combat the problem of low birth weight. Evidence of effectiveness will be only one component of information considered within the policy decision-making process.

Findings

The following systematic reviews and meta-analyses were included in the HDA Evidence Base:

HDA Evidence Base papers

Atallah, A. N., Hofmeyr, G. J. and Duley, L. (2001). Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems (Cochrane Review).

In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Makrides, M. and Crowther, C. A. (2001). Magnesium supplementation in pregnancy (Cochrane Review).

In: *The Cochrane Library*, Issue 4. Update Software: Oxford.

A number of other Cochrane reviews were identified, but these did not fulfil several of the quality criteria of a standard Cochrane review – for example, two named reviewers, description of inclusion criteria and details of search strategy. Most of these reviews were last updated between 1996 and 1998, and the protocol for Cochrane reviews has developed since then.

In addition, de Onis et al. (1998) and Villar et al. (1998) carried out systematic reviews by including the randomised controlled trials from the Cochrane Pregnancy and Childbirth Database plus additional trials published since the most recent update of the Cochrane reviews. These extra trials were obtained by contacting the authors of the systematic reviews. However, the de Onis et al. (1998) and Villar et al. (1998) reviews were considered to be of lower quality due to their inability to form a clear progression of argument from results, through discussion and into a conclusion. They were not considered appropriate for the HDA Evidence Base but have been used as supplementary papers to add further insights and to inform discussion.

Other material

Other literature or narrative reviews have informed the context and commentary in this evidence briefing and are listed overleaf. However, these papers have not met the systematicity, transparency and relevance criteria for the HDA Evidence Base.

Supplementary papers

de Onis, M., Villar, J. and Gülmezoglu, M. (1998). Nutritional interventions to prevent intrauterine growth retardation: evidence from randomised controlled trials. *European Journal of Clinical Nutrition* 52 (S1): S83-S93.

Gülmezoglu, A. M. and Hofmeyr, G. J. (2001). Maternal nutrient supplementation for suspected impaired fetal growth (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Kramer, M. S. (2001a). Balanced protein/energy supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Kramer, M. S. (2001b). Isocaloric balanced protein supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Kramer, M. S. (2001c). High protein supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Kramer, M. S. (2001d). Nutritional advice in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4. Update Software: Oxford.

Mahomed, K. (2001a). Iron and folate supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 2. Update Software: Oxford.

Mahomed, K. (2001b). Folate supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Mahomed, K. (2001c). Zinc supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 4. Update Software: Oxford.

Mahomed, K. and Gülmezoglu, A. M. (2001). Vitamin D supplementation in pregnancy (Cochrane Review). In: *The Cochrane Library*, Issue 3. Update Software: Oxford.

Villar, J., Gülmezoglu, A. M. and de Onis, M. (1998). Nutritional and antimicrobial interventions to prevent preterm birth: an overview of randomised controlled trials. *Obstetrical and Gynecological Survey* 53: 575-85.

Generally, there appears to be a dearth of high quality systematic reviews relating to nutrition and low birth weight. The findings of the reviews not included in the HDA Evidence Base provide conflicting findings and conclusions, often between and within each review. There is an urgent need for more systematic reviews to be undertaken and existing reviews to be updated.

As shown in Table 2, the studies included in the review-level evidence were conducted in a variety of countries. This means the trials reviewed were carried out in both developed and developing countries, where the health and social conditions and environments differ enormously. The quality of the studies and sample sizes investigated were also diverse. This had implications for the reported evidence of effectiveness of interventions between papers and will be discussed in greater detail later in this evidence briefing.

Full discussion of the findings of the review-level evidence of nutritional interventions follows after Table 2, on p34.

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight ■ = HDA Evidence Base papers

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Calcium supplementation for preventing hypertensive disorders	Atallah et al. (2001)	Ten studies – all double blind, placebo controlled trials. Date of last search: February 2000	Hospitals in Argentina, USA, Australia, Ecuador, India	9,439 women (data from eight trials) nulliparous women recruited at 20-24 weeks gestation	2g calcium taken daily until birth	'The data included in this review support calcium supplementation for women at high risk of gestational hypertension, and in communities with low dietary calcium intake. Optimum dosage requires further investigation'
Magnesium supplementation	Makrides and Crowther (2001)	Seven randomised controlled trials. Date of last search: June 2001	Angola, Austria, China, Hungary, Memphis and Mississippi (USA), Zurich (Switzerland)	2,689 women, two trials recruited women with high risk pregnancies	Magnesium was orally administered prior to the 25th week of gestation	'There is not enough high quality evidence to show that dietary magnesium supplementation during pregnancy is beneficial'
Balanced protein/energy supplementation	Kramer (2001a)	13 controlled trials of variable quality. Date of last search: January 2000	Taiwan, Scotland, the Gambia, Wales, India, Indonesia (East Java), Columbia (Bogota), South Africa, USA (North Carolina and New York), England. Five trials were conducted in poor, slum or low income areas	3,268 women (data from 12 trials). Two trials recruited women at risk of LBW, six trials recruited women with poor, marginal diets 'nutritionally vulnerable'	Energy/protein supplementation in which the protein content was balanced (less than 25% of total energy content). Lack of detail on supplementation methods – however, one trial used biscuits and another milk	No conclusions drawn in relation to IUGR. Kramer (2001a) concluded that the evidence for preterm birth was insufficient to evaluate the potential benefits for pregnant women or their infants
Balanced protein/energy supplementation	de Onis et al. (1998)	Seven controlled trials which reported IUGR data identified in Kramer (2001a). Databases searched up to March 1997	Taiwan, Wales, India, Indonesia (East Java), Columbia (Bogota), USA (New York), Thailand. Four trials conducted in poor, slum or low income areas	2,811 women (data from six trials)	Energy/protein supplementation in which the protein content was balanced (less than 25% of total energy content). Lack of detail on supplementation methods – however, one trial used milk protein, another milk tokens and one trial provided sesame cake, jaggery and oil	Despite reporting a non-statistically significant decrease in SGA babies, the authors categorised balanced as a protein/energy supplementation as a 'nutritional intervention likely to be beneficial'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Balanced protein/energy supplementation	Villar et al. (1998)	Five controlled trials. Databases searched up to mid 1998	No information	2,436 women	No information	The authors reported that 'preterm birth rates were lower in the supplemented groups', but the finding was non-significant. There was also conflicting data between preterm birth rates and mean gestational age – therefore a major effect on reducing preterm birth seemed unlikely. Despite this discussion, the author did not draw any final conclusions
Isocaloric balanced protein supplementation	Kramer (2001b)	Three controlled trials. Date of last search: unknown but last substantive change made in August 1996	One trial conducted on low income women in Chile. No information on the other two trials	966 women recruited at less than 20 weeks gestation	Isocaloric protein supplementation (protein <25% of total energy content). Lack of detail on supplementation methods – however, one trial used powdered milk	Kramer (2001b) suggested that 'balanced protein supplementation alone was unlikely to be of benefit to pregnant women or their infants'. The author continued: 'The possibility that isocaloric protein supplementation actually impaired foetal growth cannot be dismissed.' As a result, future trials could not be recommended
Isocaloric balanced protein supplementation	de Onis et al. (1998)	One controlled trial. Databases searched up to March 1997	Trial conducted in nine prenatal clinics in Santiago, Chile	1,135 low income underweight pregnant women	Experimental supplement of powdered milk containing 498kcal, 27.9% protein, 26% fat, 38% carbohydrates plus vitamins and minerals	Such supplements (ie without energy supplementation) may be harmful, even for malnourished women
High protein supplementation	Kramer (2001c)	Two controlled trials. Date of last search: unknown but last substantive change made in August 1996	India and New York, USA	1,076 women. One trial recruited women aged 25-40 years at 36 weeks gestation engaged in manual labour, the other trial recruited black women at less than or equal to 30 weeks gestation at risk for LBW	Protein/energy supplementation in which the protein provided \leq 25% of its total energy content	The author concluded that 'the available evidence provides no justification for prescribing high protein nutritional supplements to pregnant women. Not only do such supplements appear to lack beneficial effects, the evidence suggests that they may even be harmful'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
High protein supplementation	de Onis et al. (1998)	One controlled trial. Databases searched up to March 1997	Harlem, New York City, USA	1,051 low income black women 'at risk' for LBW based on established criteria	Experimental supplement of 470kcal, 40g protein plus vitamins and minerals per day	Such high protein supplements may be harmful, even for malnourished women
Nutritional advice in pregnancy	Kramer (2001d)	Four controlled trials. Date of last search: unknown but last substantive change made in April 1996	Rural Greece – the settings for the three other trials were not stated	1,108 women recruited at less than 20/21 or 27 weeks gestation	Two trials provided advice to women to increase the energy and protein content of the diet. One trial gave nutrition classes and the remaining trial counselled to improve the 'quality' of the diet	Outcome data on preterm birth and foetal growth were only reported in one trial, therefore the impact on birth weight cannot be judged from the available trials. Despite this lack of evidence, it was noted that 'the provision of nutritional advice was unlikely to be of major importance'
Nutritional advice in pregnancy	de Onis et al. (1998)	One experimental nutrition education trial. Methodological quality was not high. Databases searched up to March 1997	Florina, rural county of northern Greece	568 low SES women, the majority enrolled at less than 21 weeks gestation and all before 27 weeks gestation	Experimental nutrition education to improve nutrient value of diet through home visits every two weeks by trained nurses	Nutritional counselling did not show an effect in reducing the rate of SGA births; however, the author concluded that 'the implications for foetal health cannot be judged from the available evidence'
Nutritional advice in pregnancy	Villar et al. (1998)	One controlled trial. Databases searched up to mid 1998	No information	502 women	No information	Data from one trial showed a statistically significant reduction in preterm delivery. Results were limited due to methodological issues and no conclusions were drawn
Combined iron and folate supplementation	Mahomed (2001a)	Eight controlled trials. Date of last search: unknown but last substantive change made in August 1997	Burma, Nigeria, UK	5,449 women recruited prior to 28 weeks gestation, usually recruited at the first antenatal clinic visit. Women were recruited if the initial haemoglobin level was less than 10g/dl	The usual supplemental dose was around 100mg elemental iron plus 350µg folic acid taken orally every day	'There was no detectible effect on preterm delivery or low birth weight'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Iron supplementation	de Onis et al. (1998)	Two trials. One trial had small sample sizes and the other had possible bias. Databases searched up to March 1997	Finland, USA. One trial conducted in a university, the other was a multi-centre trial using maternity centres	3,016 healthy women recruited at less than 16 weeks gestation	One trial used daily multivitamin/minerals with (65mg) and without iron. The other trial provided a single daily dose of 100mg elemental iron, dosage determined by 51 midwives	'There seems to be no evidence currently to recommend routine (iron supplementation to all women throughout pregnancy) as opposed to selective iron supplementation (prescribed only to women with a low iron status) in well nourished populations and there are inadequate data from populations where iron deficiencies are common; thus it is urgent that it be adequately tested in anaemic populations'
Iron supplementation	Villar et al. (1998)	One controlled trial. Databases searched up to mid 1998	Finland	2,694 well nourished women	No information	'Iron supplementation is warranted for the prevention of maternal anaemia in populations with a high prevalence of anaemia but not as a preventative measure for preterm delivery'
Folate supplementation	Mahomed (2001b)	21 controlled trials of varying methodological quality (data from single trials with relatively small sample sizes). Date of last search: unknown but last substantive change made in May 1997	Australia, Burma, Chile, Denmark, France, India, Nigeria, South Africa, Switzerland, Thailand, UK	10,470 women recruited before 28 weeks gestation, usually at their first antenatal visit, if haemoglobin over 10g/dl	In most trials the folate dose was 500µg per day taken orally for approximately 16 weeks	The author drew no conclusions about its effectiveness in preventing low birth weight
Folate supplementation	de Onis et al. (1998)	Five trials of low quality. Databases searched up to March 1997	Nigeria, South Africa, Australia, India, Denmark. Women mainly recruited through antenatal care	1,165 women	In most trials the folate dose was 500µg per day taken orally	Reported a statistically significant reduction in the incidence of term LBW, based on the findings of five trials. However, the authors noted that most of the trials had methodological problems and were performed in populations where iron supplementation was also routine. Despite these positive findings, the authors categorised routine folate supplementation as a 'nutritional intervention unlikely to be beneficial'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Folate supplementation	Villar et al. (1998)	Four controlled trials. Databases searched up to mid 1998	No information	1,425 women	No information	Based on the findings of four trials, no beneficial effects were found. Concluded that the provision of routine folate during antenatal care for the prevention of preterm birth was not justified
Zinc supplementation	Mahomed (2001c)	Seven randomised controlled trials with many being double blind. Date of last search: unknown but last substantive change made in May 1997	Denmark, UK, USA	1,486 women (data from five trials) recruited before 20 weeks gestation (one trial recruited before 27 weeks)	Between 20-62mg of elemental zinc per day taken orally	Found no evidence of overall benefit from routine zinc supplementation and 'there was insufficient evidence to evaluate fully the effect of zinc supplementation during pregnancy'
Zinc supplementation	de Onis et al. (1998)	Four double blind trials. Databases searched up to March 1997	Alabama and Los Angeles, USA, London and Bristol, UK. Trials were performed in populations with varied zinc nutritional status and at risk from poor foetal growth	1,343 women. One trial recruited women with low plasma zinc levels, another recruited women at risk of delivering an SGA baby	Daily supplement of zinc between 20 and 25mg	Showed a 23% non-significant reduction in term low birth weight and concluded that 'the available data provide no convincing case for routine zinc supplementation during pregnancy'
Zinc supplementation	Villar et al. (1998)	Four controlled trials. Databases searched up to mid 1998	No information	1,333 women. One trial recruited women with low plasma zinc levels	No information	Data showed zinc supplementation had no impact on preterm birth; however, a single study conducted in a population with low plasma zinc levels did report a beneficial effect on birth weight increases, but not preterm birth. Concluded that 'the routine provision of zinc during antenatal care for the prevention of preterm birth was not justified, but further research was warranted'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Vitamin D supplementation	Mahomed and Güllmezoglu (2001)	Two randomised controlled trials. Date of last search: October 1998	France, UK	232 women (white women in NW France and first generation Asian women in London)	One trial randomised to three groups, one receiving 1,000 IU vitamin D per day in the last trimester, another receiving a single dose of 5mg (200,000 IU) and control group. The other trial administered 1,000 IU vitamin D per day during the third trimester until delivery	Two trials provided conflicting results regarding the impact of vitamin D supplementation on the number of low birth weight infants. The review concluded that 'there was not enough evidence to evaluate the effect of vitamin D supplementation during pregnancy'
Vitamin D supplementation	de Onis et al. (1998)	One controlled trial run over two years to avoid confounding variables such as sunlight hours. Databases searched up to March 1997	London	126 first generation immigrant Asian women	1,000 IU vitamin D daily throughout the last trimester until term	Reported on a single study that showed a non-significant effect on foetal growth. However, the authors concluded that 'vitamin D supplementation suggests a potential beneficial effect on foetal growth in vulnerable groups such as pregnant women living in sunless climates'. Despite this conflicting finding and conclusion, this intervention was categorised by the authors as 'a nutritional intervention unlikely to be beneficial'
Fish oil supplementation	de Onis et al. (1998)	Two trials. Databases searched up to March 1997	Aarhus, Denmark, Leeds, UK. Subjects recruited by the main midwife or antenatal clinic	766 women. One trial recruited women at 30 weeks gestation	Daily supplement of prophylactic fish oil and fish and olive oil capsules	Concluded that 'it was not possible to make any firm conclusions about the role of fish oil in pregnancy based on the limited available evidence'. Overall, they categorise fish oils as a 'nutritional intervention unlikely to be beneficial'

Table 2: Characteristics of the review-level evidence of nutritional interventions to prevent low birth weight (cont.)

Intervention	Author and year	Number and type of studies included	Setting	Participants	Protocol	Conclusion
Fish oil supplementation	Villar et al. (1998)	Two trials. Databases searched up to mid 1998	London, UK	5,550 women	The experimental group received vitamins and minerals as well as fish oil	From two studies, there was a statistically significant reduction in preterm birth rates with fish oil supplementation. The authors suggest that these results are 'promising' but urge caution due to the age of the dominant study and the fact that other nutrients were included in the intervention
Maternal nutritional supplements	Gülmezoglu and Hofmeyr (2001)	Three studies, all placebo controlled trials. Date of last search: December 1999	No information	121 women with suspected impaired foetal growth	Nutrients (calf blood extract, carnitine, aminoacid solutions and glucose) administered to the mother orally, parenterally or by amnioinfusion to the amniotic cavity	Findings revealed no difference in the number of SGA infants in mothers who had received nutritional supplementation compared to those who did not. The authors did not reach any conclusion on the use of such supplements in pregnant women with suspected impaired foetal growth

Calcium supplementation

Three systematic reviews examined the effectiveness of calcium supplementation during pregnancy. The proposed mechanism of action for calcium supplementation is via a reduction in hypertension (which may reduce rates of pregnancy induced hypertension and pre-eclampsia), resulting in prolonged gestation and hence higher birth weight. It is important to note that dietary calcium intakes in the female UK population are low, with 27% of 16-18 year olds and 10% of 19-50 year olds consuming an intake below the Lower Reference Nutrient Intake (400mg a day) (Gregory et al., 1990).

The Cochrane review by Atallah et al. (2001) predominantly focused on women at high risk of hypertensive disorders but also included those of low or average risk. Ten studies were included, all well-designed, double blind, placebo controlled trials comparing at least 1g daily of calcium during pregnancy with the placebo (from, at the latest, 34 weeks of pregnancy). The results found no overall effect on preterm delivery, but for those women at high risk of developing hypertension, there was a reduction in the incidence of preterm births with calcium supplementation (four trials, 568 women: relative risk (RR): 0.42, 95% CI: 0.23-0.78). Furthermore, calcium supplementation was found to reduce the incidence of low birth weight (seven trials, 6,491 women: RR: 0.83, 95% CI: 0.71-0.98). Again, the effect seemed to be greatest for women at high risk of hypertension (two trials, 449 women: RR: 0.45, 95% CI: 0.22-0.95) but this was a post hoc subgroup analysis. No side effects of calcium supplementation were noted by the authors in any of the included trials. The authors concluded that 'the data included in this review support calcium supplementation for women at high risk of gestational hypertension, and in communities with low dietary calcium intake (less than 900mg/day)*. Further randomised trials should concentrate on women at high risk of gestational hypertension, and communities with low dietary calcium intake, and the effect on substantive outcomes should be determined'. The authors did not draw any conclusions on the reduced incidence of low birth weight in the calcium supplemented groups.

De Onis et al. (1998) and Villar et al. (1998) also investigated the effectiveness of calcium supplementation

during pregnancy. However, these authors disaggregated the low birth weight data (based on a previous edition of the Cochrane review) and conducted separate analyses for the two main contributors of low birth weight: IUGR and preterm birth. Their findings conflicted with those of Atallah et al. (2001), but we gave precedence to the evidence from the latest Cochrane review as this was the most up-to-date and rigorous source of evidence.

Based on the evidence from the included HDA Evidence Base papers: there is evidence to support the effectiveness of calcium supplementation for a reduction in preterm birth and the incidence of low birth weight in pregnant women, especially those at risk of hypertensive disorders.

Magnesium supplementation

In a Cochrane review by Makrides and Crowther (2001), the authors carried out a meta-analysis of seven trials (involving 2,689 women) to investigate the effects of magnesium supplementation on pregnancy outcomes. Magnesium was orally administered prior to the 25th week of gestation.

Six of the seven trials randomly allocated women to either an oral magnesium supplement or a control group, while the seventh and largest trial of 985 women had a cluster design where randomisation was by study centre. The meta-analysis was conducted with and without the cluster trial.

Findings from the meta-analysis of all seven trials revealed that magnesium treatment was associated with a lower frequency of preterm birth (less than 37 weeks) (RR: 0.73, 95% CI: 0.57-0.94) compared with placebo. In addition, magnesium treatment was associated with a reduced risk of low birth weight (defined as birth weight less than 2-2.5kg by the authors) (RR: 0.67, 95% CI: 0.46-0.96) and of SGA babies (RR: 0.70, 95% CI: 0.53-0.93) compared with placebo.

However, as stated earlier, one study used a clustered randomisation technique. When the meta-analysis was conducted to exclude this trial (where bias was likely to favour a positive result), the effects of magnesium supplementation on the frequencies of preterm birth, low birth weight and SGA were no different from the placebo.

* The UK calcium Reference Nutrient Intake for women aged 19-50+ years is 700mg per day.

The authors concluded that 'there is not enough high quality evidence to show that dietary magnesium supplementation during pregnancy is beneficial. Further trials are warranted and should be of high quality, especially regarding the concealment of allocation, the unit of randomisation, selection of placebo, blinding of outcome assessments and minimal losses to follow-up.'

Again, de Onis et al. (1998) and Villar et al. (1998) also investigated the effectiveness of magnesium supplementation during pregnancy and reported conflicting findings. However, as with calcium supplementation, we gave precedence to the evidence from the latest Cochrane review as this was the most up-to-date and rigorous source of evidence.

Based on the evidence from the included HDA Evidence Base papers: there is a lack of evidence to support the routine use of magnesium supplementation during pregnancy to prevent low birth weight.

Balanced protein/energy supplementation

Three lower quality* reviews have investigated the effectiveness of balanced protein/energy supplementation for pregnant women (the supplement was considered balanced if the protein content was less than 25% of the total energy content) (Kramer, 2001a; de Onis et al., 1998; Villar et al., 1998).

IUGR (SGA)

Kramer (2001a) identified 13 trials of variable quality and found that supplementation was associated with modest increases in foetal growth (birth weight increase, weighted mean difference 25g, 95% CI: 4-55g). Furthermore, a reduction in risk of SGA birth was reported (odds ratio (OR): 0.64, 95% CI: 0.53-0.78). The author drew no conclusion from these results. De Onis et al. (1998) analysed seven of the 13 trials (those that reported IUGR data) identified in Kramer (2001a). The authors' meta-analysis showed that supplementation caused a non-statistically significant decrease in SGA babies (OR: 0.77, 95% CI: 0.58-1.01). Despite this non-significant finding, the authors categorised balanced protein/energy supplementation as a 'nutritional intervention likely to be beneficial'. No other conclusions were drawn by the authors on the effectiveness of supplementation on IUGR or SGA birth.

There is conflicting low quality* review-level evidence regarding the effectiveness of balanced protein/energy supplementation in preventing IUGR and SGA births.

Preterm birth

Based on the same 13 trials, Kramer (2001a) found that no significant effects were detected for preterm birth in the supplemented group. The author concluded that the evidence was insufficient to evaluate the potential benefits for pregnant women or their infants. In comparison, Villar et al. (1998) analysed five of the 13 trials from the Cochrane review (which reported preterm birth data). The authors reported that 'preterm birth rates were lower in the supplemental groups', but the finding was non-significant (RR: 0.83, 95% CI: 0.65-1.06). There was also conflicting data between preterm birth rates and mean gestational age; therefore a major effect on reducing preterm birth seemed unlikely. Despite this discussion, the author did not draw any final conclusions or make any recommendations for future research.

There is conflicting low quality* review-level evidence regarding the effectiveness of balanced protein/energy supplementation in preventing preterm birth.

Isocaloric balanced protein supplementation

Three lower quality* systematic reviews (Kramer, 2001b; de Onis et al., 1998; Villar et al., 1998) examined the effectiveness of providing pregnant women with isocaloric protein supplements on gestational weight gain and pregnancy outcome. The protein supplement was considered isocaloric when the protein replaced an equal quantity of non-protein energy and had less than 25% of its total energy content as protein. The Cochrane review by Kramer (2001b) identified three trials (involving 966 women) of varying methodological quality and size.

Results showed a statistically significant increased risk of SGA births with isocaloric protein supplementation (one trial, OR: 1.61, 95% CI: 1.20-2.14) but there were no

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

effects on mean gestational age or preterm birth (three trials, RR: 1.05, 95% CI: 0.69-1.60). The author found that the small size of two of the three trials made it difficult to judge their findings.

In conclusion, Kramer (2001b) suggested that 'balanced protein supplementation alone was unlikely to be of benefit to pregnant women or their infants.' The author continued, 'the possibility that isocaloric protein supplementation actually impaired foetal growth cannot be dismissed'. As a result, future trials could not be recommended.

The review by de Onis et al. (1998) is in agreement and concludes that such supplements (ie without energy supplementation) may be harmful, even for malnourished women. Finally, Villar et al. (1998) lists the quantitative preterm birth data in a table but provides no further discussion of these findings in the text.

There is evidence that isocaloric balanced protein supplementation may be harmful. There is no high quality review-level evidence that isocaloric balanced protein supplementation is effective for the prevention of SGA and preterm birth. There is, however, low quality* review-level evidence that isocaloric balanced protein supplementation of pregnant women is ineffective for the prevention of SGA and preterm births.

High protein supplementation

Three lower quality* systematic reviews (Kramer, 2001c; de Onis et al., 1998; Villar et al., 1998) investigated the effects of providing pregnant women with high protein nutritional supplements on gestational weight gain and pregnancy outcome. The protein content of the supplement provided more than 25% of its total energy content.

Two studies involving 1,076 women were included in the Cochrane review (Kramer, 2001c) varying in methodological quality and size. Neither trial provided evidence of benefit on foetal growth (absolute weight); moreover, the mean birth weight was 58.4g lower. The author concluded that 'the available evidence provides no justification for prescribing high protein

nutritional supplements to pregnant women. Not only do such supplements appear to lack beneficial effects, the evidence suggests that they may even be harmful.'

The review by de Onis et al. (1998) agreed, and concluded that such high protein supplements may be harmful, even for malnourished women. Finally, Villar et al. (1998) listed the quantitative preterm birth data in a table but provided no further discussion of these findings in the text.

There is evidence that high protein supplementation may be harmful. There is no high quality review-level evidence that high protein supplementation is effective for the prevention of low birth weight. There is, however, low quality* review-level evidence that high protein supplementation in pregnant women is ineffective for the prevention of low birth weight.

Nutritional advice

Another lower quality* systematic review by Kramer (2001d) assessed the effects on pregnancy outcome of advising pregnant women to increase their energy and protein intakes. Four trials involving 1,108 women were included, although the overall methodological quality of these trials was not high.

Kramer (2001d) found that advice to increase energy and protein intakes was successful in achieving these dietary goals, although no outcome data on energy and protein intakes were reported. The review did state, however, that increases in energy and protein intakes were lower than those reported in trials of actual protein/energy supplementation. Outcome data on preterm birth and foetal growth were only reported in one trial, therefore the impact on birth weight cannot be judged from the available trials. Despite this lack of evidence, it was noted that 'the provision of nutritional advice was unlikely to be of major importance'.

De Onis et al. (1998) and Villar et al. (1998) also reported on this topic area. Although de Onis et al. (1998) reported the same findings as Kramer (2001d) (OR: 1.0, 95% CI: 0.48-2.08), that nutritional counselling did not show an effect in reducing the rate of SGA births, de Onis et al. concluded differently that 'the implications for foetal health cannot be judged from the available evidence'.

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

Finally, Villar et al. (1998) investigated one trial (that reported preterm birth outcome data) and showed a statistically significant reduction in preterm delivery of 55% (RR: 0.45, 95% CI: 0.22-0.92). In a discussion, the authors commented that the results were limited because of methodological issues, but unfortunately they did not draw any conclusions or make any recommendations for future research.

There is conflicting evidence from low quality* reviews regarding the effectiveness of nutritional advice for the prevention of low birth weight. No conclusions about benefit or harm could be drawn.

Combined iron and folate supplementation

A lower quality* Cochrane review by Mahomed (2001a) investigated the effects of combined routine iron and folate supplementation on pregnancy outcome. The usual combined iron and folate supplementation dose was about 100mg elemental iron plus 350µg folic acid taken daily, and treatment was provided for 16 weeks or more. Eight single small trials involving 5,449 women (haemoglobin levels greater than 10g/dl) were included, but there was a lack of data from these trials on the effects on foetal outcome. The author concluded that 'there was no detectible effect on preterm delivery or low birth weight'.

There is a lack of review-level evidence regarding the routine use of combined iron and folate supplementation for the prevention of low birth weight. No conclusions about benefit or harm could be drawn.

Iron supplementation

De Onis et al. (1998) and Villar et al. (1998) reviewed the impact of iron supplementation alone on pregnancy outcomes. De Onis et al. (1998) identified two trials conducted in well-nourished women from developed countries and found that routine iron supplementation resulted in no substantive differences in pregnancy outcome (IUGR) (OR: 0.92; 95% CI: 0.59-1.43). The authors concluded that 'there seems to be no evidence

currently to recommend routine (iron supplementation to all women throughout pregnancy) as opposed to selective iron supplementation (prescribed only to women with a low iron status) in well nourished populations and there are inadequate data from populations where iron deficiencies are common; thus it is urgent that it be adequately tested in anaemic populations'. However, conducting a controlled trial of this nature does raise ethical issues, as this would involve the non-treatment of pregnant anaemic women.

Villar et al. (1998) identified only a single trial where preterm birth was an outcome measure. Results showed that there was a non-significant decrease in preterm birth (RR: 0.71, 95% CI: 0.48-1.06), but there was also an unexpected increase in still births and neonatal deaths in the iron supplemented group. As a result, the author concluded that 'iron supplementation is warranted for the prevention of maternal anaemia in populations with a high prevalence of anaemia but not as a preventive measure for preterm delivery'.

In the UK, 6% of women aged 18-24 years, 4% of women aged 25-34 years and 4% of women aged 35-49 years had a low iron status (haemoglobin less than 11.0g/dl) (Gregory et al., 1990). In agreement with Villar et al. (1998), we do not recommend further research within the UK on iron supplementation as a preventive measure for low birth weight. Other areas of research should be a priority (see 'Gaps in the evidence base', p41).

Based on low quality* review-level evidence, there is a lack of evidence to support the use of routine iron supplementation for preventing low birth weight.

Folate supplementation

A lower quality* Cochrane review (Mahomed, 2001b) assessed the effect of folate supplementation in pregnant women with normal initial levels of haemoglobin. Twenty-one studies were included of varying methodological quality (data from single trials with relatively small sample sizes). In most trials the folate dose was 500µg per day for a duration of approximately 16 weeks.

The review found that apart from a possible non-significant reduction in the incidence of low birth weight,

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

folate supplementation appeared to have no measurable effect on any other pregnancy outcomes. Despite this, the author drew no conclusions about its effectiveness in preventing low birth weight, suggesting that better controlled trials in populations in which folate deficiency are common should be a priority.

De Onis et al. (1998) and Villar et al. (1998) also investigated the effectiveness of folate supplementation. The results from the five trials included by de Onis et al. (1998) showed a statistically significant reduction in the incidence of term low birth weight. However, the authors noted that most of the trials had methodological problems and were performed in populations where iron supplementation was also routine. Despite these positive findings, the authors categorised routine folate supplementation as a 'nutritional intervention unlikely to be beneficial'. Finally, it was suggested that 'better controlled trials in populations in which folate deficiency is common are needed before any firm recommendations can be made'.

Villar et al. (1998) reported on four trials that assessed the impact of folate supplementation on preterm birth outcomes. No beneficial effects were found (RR: 1.03, 95% CI: 0.71-1.49). The authors concluded that the provision of routine folate supplementation during antenatal care for the prevention of preterm birth was not justified.

In the UK, 4% of women aged 16-50 years have dietary folate intakes below the Lower Reference Nutrient Intake (100 microgrammes (μg) a day) (Gregory et al., 1990). In agreement with Villar et al. (1998), we do not recommend further research within the UK on folate supplementation as a preventive measure for low birth weight. Other areas of research should be a priority (see 'Gaps in the evidence base', p41).

There is conflicting low quality* review-level evidence regarding the effectiveness of folate supplementation in preventing low birth weight.

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

Zinc supplementation

Three lower quality reviews* (Mahomed, 2001c; de Onis et al., 1998; Villar et al., 1998) evaluated the effects of zinc supplementation during pregnancy. Seven trials were included by Mahomed (2001c), where 20-62 milligrammes (mg) of elemental zinc was prescribed from at least 26 weeks gestation. Significantly lower rates of preterm delivery were observed in the supplemented groups. However, there appeared to be an inconsistency between trials regarding the effects on pregnancy outcome. This may be related to the varied population characteristics of the pregnant women recruited to the trials. Mahomed (2001c) reported that there might be some benefit in a selected group of pregnant women, but there was no evidence of overall benefit from routine zinc supplementation. Moreover, 'there was insufficient evidence to evaluate fully the effect of zinc supplementation during pregnancy'. The author noted that further trials were needed, especially in regions where there may be a zinc deficiency among pregnant women.

De Onis et al. (1998) identified four studies, involving 1,343 women, of zinc supplementation (20-25mg per day). A meta-analysis showed a 23% non-significant reduction in term low birth weight (OR: 0.77, 95% CI: 0.54-1.11). The authors concluded that 'the available data provide no convincing case for routine zinc supplementation during pregnancy'. The authors also noted that more trials were needed in selected communities at high risk of being zinc deficient.

Finally, Villar et al. (1998) included four trials in their analysis with preterm birth outcome data. Overall data showed zinc supplementation had no impact on preterm birth (RR: 0.76, 95% CI: 0.51-1.10). However, a single study conducted in a population with low plasma zinc levels did report a beneficial effect on birth rate increases, but not preterm birth. The authors concluded that 'the routine provision of zinc during antenatal care for the prevention of preterm birth was not justified, but further research was warranted'.

The measurement of zinc deficiency within the UK is problematic (Gibson, 1990) – the only available indicator of zinc status is dietary zinc intake. In the UK, 6% of women aged 16-18 years and 4% of women aged 19-50 years have zinc intakes below the Lower Reference Nutrient Intake (4.0mg a day) (Gregory et al., 1990).

Despite the authors' recommendation for further research expressed in the reviews above, we do not recommend further research within the UK on zinc supplementation to prevent low birth weight. Other areas of research should be a priority (see 'Gaps in the evidence base', p41).

There is a lack of review-level evidence to support the use of routine zinc supplementation in pregnant women for the prevention of low birth weight.

Vitamin D supplementation

In a lower quality* Cochrane review, Mahomed and Gülmezoglu (2001) assessed the effects of vitamin D supplementation on pregnancy outcome. Two trials involving 232 women were included. The trials provided conflicting results regarding the impact of vitamin D supplementation on the number of low birth weight infants. This could have been due to chance given the small numbers of pregnant women studied. The review concluded that 'there was not enough evidence to evaluate the effect of vitamin D supplementation during pregnancy'. Moreover, de Onis et al. (1998) reported on a single study that included IUGR outcome data. The study showed a non-significant effect on foetal growth (OR: 0.50, 95% CI: 0.20-1.26). However, the authors concluded that 'vitamin D supplementation suggests a potential beneficial effect on foetal growth in vulnerable groups such as pregnant women living in sunless climates'. Despite this conflicting finding and conclusion, this intervention was categorised by the authors as 'a nutritional intervention unlikely to be beneficial'.

There is conflicting low quality* review-level evidence regarding the effectiveness of vitamin D supplementation in preventing low birth weight.

Fish oil supplementation

De Onis et al. (1998) and Villar et al. (1998) have evaluated the effect of fish oil supplementation during pregnancy, each review looking at two trials. The results of de Onis et al. (1998) generally showed no difference in effectiveness between the fish oil supplemented groups

and controls. The exception was fish oil versus olive oil, where fish oil produced an increased mean birth weight of 126g (95% CI: 19.3-232.7g). The authors concluded that 'it was not possible to make any firm conclusions about the role of fish oil in pregnancy based on the limited available evidence'. They also noted that large RCTs were required to reliably assess the potential benefits or adverse effects. Overall, they categorise fish oils as a 'nutritional intervention unlikely to be beneficial'.

Villar et al. (1998) reports positive effects of fish oil supplementation. From two studies that included preterm birth outcomes, there was a statistically significant reduction in preterm birth rates with fish oil supplementation (RR: 0.83, 95% CI: 0.75-0.92). The authors suggest that these results are 'promising' but urge caution due to the age of the dominant study and the fact that other nutrients were included in the intervention. They call for more RCTs in this area. Despite the authors' recommendation for further research, we do not recommend further research within the UK on fish oil supplementation as a means of preventing low birth weight. Other areas of research should be a priority (see 'Gaps in the evidence' base, p41). Furthermore, the Department of Health has advised that women should not consume fish oil supplements during pregnancy due to the possibility of high levels of contaminants.

There is conflicting low quality* review-level evidence regarding the use of fish oil supplementation in the prevention of low birth weight.

Atypical maternal supplementation (protein free calf blood extract, carnitine, intravenous glucose or oral galactose treatment)

A Cochrane review (Gülmezoglu and Hofmeyr, 2001) assessed the effects of atypical maternal nutritional supplementation (protein-free calf blood extract, carnitine, intravenous glucose or oral galactose treatment) on foetal growth and birth outcomes. The three studies involved 121 women with suspected impaired foetal growth.

The findings revealed no difference in the number of SGA infants in mothers who had received nutritional supplementation compared to those who did not. Although the results from two of the three trials showed some benefit in terms of outcomes studied, both had small sample sizes and methodological limitations.

* Quality was assessed by our critical appraisal form (Appendix 2) using the criteria of systematicity, relevance and transparency.

Therefore the authors did not reach any conclusion on the use of such supplements in pregnant women with suspected impaired foetal growth.

There is a lack of evidence regarding the effectiveness of atypical maternal nutritional supplementation (protein free calf blood extract, carnitine, intravenous glucose or oral galactose treatment) in pregnant women with suspected impaired foetal growth. No conclusions about benefit or harm could be drawn.

The Special Supplemental Nutrition Program for Women, Infants and Children (WIC), and the Expanded Food and Nutrition Education Program (EFNEP)

No review-level evidence about the WIC or EFNEP programmes satisfied the critical appraisal process for inclusion in this briefing. However, because of their importance and the many individual papers describing promising practice, a section outlining the contribution of these programmes has been included.

The WIC programme has been funded by the US Department of Agriculture since 1972 and is intended to provide food supplements for low income pregnant and post-partum women, and children under five years of age, who are considered to be at nutritional risk. The purpose of the WIC programme is to improve pregnancy outcomes, including rates of prematurity and infant and foetal mortality. The programme is administered at state level, delivered by a wide variety of agencies, and gives priority to geographical areas with high rates of infant mortality, low birth weight and low income.

In 1997, more than seven million people benefited from WIC each month with children being the largest group of recipients (3.8 million). Furthermore, 98% of eligible infants receive WIC. Findings from evaluations of WIC have shown improved birth and diet-related outcomes such as a reduction in rates of low and very low birth weights of 25% and 44% respectively (Owen and Owen, 1997). There are also estimated savings in healthcare costs of \$1.77 to \$3.13 for every dollar spent on WIC. Another analysis of WIC found that the incidence of low birth weight was 13.1% for non-participants and 10.2% for WIC participants (Brown et al., 1996).

EFNEP was established in 1969, again by the US Department of Agriculture, to provide limited-resource families with food and nutrition education through individually tailored home education sessions. Over the past 30 years, EFNEP has become the largest federally funded programme exclusively offering nutrition education and serves about 200,000 families with young children per year. EFNEP operates in all 50 US states and in several territories.

EFNEP targets two primary audiences: low income youth, and low income families with young children; the aim being to help low income audiences acquire the knowledge, skills, attitudes and changed behaviour desirable for nutritionally sound diets. Since its inception, EFNEP has reached 23 million families and young people. EFNEP is delivered as a series of lessons, by para-professionals and volunteers, many of whom are indigenous to the population (this approach is an area of emerging interest in the UK). The hands-on, learn-by-doing approach allows the participants to gain the practical skills necessary to make positive behaviour changes. Data from the EFNEP Evaluation/Reporting System show that 87% of participants improved in one or more nutrition practice (eg making healthy food choices, planning meals, reading nutrition labels etc). A recent cost benefit analysis of the Virginia EFNEP found that for every dollar spent in implementing the programme, there is a \$10.64 benefit due to reduced healthcare costs (Rajgopal et al., 2002).

A review of effectiveness of interventions to promote healthy eating in pregnant women and women of childbearing age (van Teijlingen et al., 1998) identified 12 published articles on WIC. The review found that these papers tended to support a beneficial effect of WIC participation, but were all confounded to a certain extent by baseline differences between the WIC and non-WIC comparison groups. In conclusion, van Teijlingen et al. (1998) agreed with the conclusion of Rush et al. (1988) in their national evaluation of the WIC programme: 'After a decade of the existence of the program, there existed too little information to judge, one way or the other, whether WIC was meeting the goals set for it by the Congress and the public.'

A systematic review of the effectiveness of food and information-based programmes such as these, and whether they might transfer to the UK, should be a high priority, but only if there is adequate literature for undertaking such a review.

Table 3: Review-level evidence on the effectiveness of nutritional interventions for the prevention of low birth weight (LBW)

Evidence of effectiveness	Current lack of evidence of effectiveness	Conflicting evidence of effectiveness	Use not recommended, evidence of potential harm
Calcium supplementation (to reduce preterm birth and LBW, especially those at risk of hypertensive disorders)	<p>Magnesium supplementation (to reduce LBW)</p> <p>Balanced protein/energy supplementation (to reduce preterm birth)</p> <p>Iron and folate supplementation (to prevent LBW)</p> <p>Iron supplementation (to prevent LBW)</p> <p>Zinc supplementation (to prevent LBW)</p> <p>Atypical maternal nutritional supplementation (protein free calf blood extract, carnitine, intravenous glucose or oral galactose treatment) (in pregnant women with impaired foetal growth)</p>	<p>Balanced protein/energy supplementation (to prevent IUGR and SGA births)</p> <p>Nutritional advice in pregnancy (to prevent LBW)</p> <p>Folate supplementation (to prevent LBW)</p> <p>Vitamin D (to prevent LBW)</p> <p>Fish oil supplementation (to prevent LBW)</p>	<p>Iso-caloric balanced protein supplementation (to prevent LBW)</p> <p>High protein supplementation (to prevent LBW)</p>

Conclusion

Table 3 summarises the effectiveness of nutritional interventions to prevent low birth weight. It highlights the lack of high quality systematic review-level evidence regarding what interventions work to prevent low birth weight. Only one intervention was found to be effective, namely calcium supplementation. Many interventions were subject to inadequate or conflicting evidence, and most are based on lower quality review-level evidence. Two interventions, isocaloric balanced protein and high protein supplementation, were found to be potentially harmful.

Based on the review-level evidence presented, the effect of nutrition on low birth weight appears unclear for nutrient supplements (except for calcium for pregnant women at risk of hypertension). The reduction of low birth weight births, and its consequent association with long-term health, is regarded as an important policy area. Further research is urgently needed to gain a greater understanding of low birth weight and how its prevalence can be reduced, particularly with multi-faceted food and information-based interventions such as WIC and EFNEP.

Gaps in the evidence base

As shown in Table 3, there appears to be an enormous gap between the problem of low birth weight and the quality and size of the trials to prevent it. The quality of the systematic reviews was also low, despite many being Cochrane reviews.

From the high quality systematic review literature, there is little clear evidence from which population-based policy and guidelines can be established. The exception is calcium supplementation, for which an investigation of its suitability for application in population-based policy is required. A number of recommendations for further research have been made, particularly in relation to the general evidence base, the specific nutrients to be studied and trial design.

Recommendations for research

General evidence base

- We question whether a single intervention is likely to reduce the rate of a multi-causal outcome like IUGR that is so dependent on socio-economic disparities. Appropriate combinations of interventions should be a priority for evaluation in the context of large methodologically sound trials (de Onis et al., 1998).
- Trials that have been conducted on food-based interventions (rather than nutrient-based), such as the Special Supplemental Nutrition Program for Women, Infants and Children (WIC) or the Expanded Food and Nutrition Education Program (EFNEP) in the USA, should be identified and the suitability of carrying out a systematic review should be assessed.
- The findings also raise questions regarding the appropriate timing and dosage of the interventions, considering that long-standing social and nutritional deprivation are difficult to overcome by a nutritional intervention during the few months in the course of a pregnancy. The majority of trials have been conducted in mid to late pregnancy which may be too late for nutrient effects to be seen. Nutritional status around the time of conception may exert a different and maybe more powerful influence on foetal growth than status in late gestation. There is an urgent need to understand how maternal nutrition before and in early pregnancy relates to foetal growth.
- There is an urgent need for more high quality systematic reviews to be written and existing Cochrane reviews updated.
- There is a complete lack of systematic review-level evidence regarding the effectiveness of interventions targeting specific socio-economic, ethnic or vulnerable groups. This is surprising given the higher prevalence of low birth weight among such groups, and there is a need to target these groups in further research.
- There is a complete lack of systematic review-level evidence regarding the effectiveness of interventions targeting women who have multiple risk factors, ie smoking, poor dietary intake and negative psychosocial factors, etc.
- There is no reported systematic review-level evidence on the cost effectiveness of nutritional interventions.

Specific nutritional interventions

The study authors made many recommendations for research within the individual systematic reviews included

in this briefing. These have been listed below; however, they specifically focus on individual nutrients. We do not recommend further research within the UK on these topics in terms of preventing low birth weight. The areas of research outlined above should take priority.

The study authors call for:

- Further randomised trials to evaluate calcium supplementation during pregnancy, concentrating on women at high risk of gestational hypertension. The effect on substantive outcomes should also be determined (Atallah et al., 2001)
- Further trials investigating magnesium supplementation (Makrides and Crowther, 2001)
- More research to assess the effectiveness of balanced protein/energy supplementation (Kramer, 2001a)
- Further evidence on iron and folate supplementation from large-scale, scrupulously conducted, randomised trials (Mahomed, 2001a)
- Adequate testing of iron supplementation in pregnancy in anaemic populations (de Onis et al., 1998)
- Better controlled folate and zinc supplementation trials in populations where deficiency is common (Mahomed, 2001b; 2001c)
- More RCTs to investigate the effectiveness of fish oil supplementation (Villar et al., 1998).

Future trial design

- It is imperative that nutritional supplementation to enhance foetal growth is investigated through high quality, well-designed randomised controlled trials with clear endpoints.
- Consideration should be given in the methodology to the concealment of allocation, the unit of randomisation, selection of placebo, blinding of outcome assessments and minimal losses to follow-up.
- More information should be provided in systematic reviews on the nutritional status of study participants, when the intervention started and how long it lasted. Systematic review objectives need to be explicit about these factors.
- Investigation is needed into what aspects of interventions appear to be effective or ineffective (eg types of setting, sources of advice, frequency of contact).
- Process/qualitative information should also be collected to allow features of effective interventions to be easily identified, and to provide cost-effectiveness data.

Concluding comments

Low birth weight is an enduring aspect of childhood morbidity, a major factor in infant mortality and has serious consequences for health in later life. The risk of low birth weight increases with lower social class. The major risk factors from a public health perspective are smoking and poor nutrition (Kramer et al., 2000).

Systematic review-level evidence suggests that significant reductions in smoking prevalence among pregnant women can be achieved by delivering cessation programmes in antenatal care settings, and that this could impact on the birth weight of babies born to such women. We need to know more about the content of these interventions. There is a need to build in follow-up to prevent relapse and to determine what additional components of intervention may increase effectiveness among those most resistant to quitting, including poorer women. This is a matter of the highest priority for public health.

The picture regarding nutritional interventions is mixed, with insufficient high quality evidence in many areas to provide clear guidance for policy-makers and practitioners. Trials of calcium supplements provide promising avenues for assessing its appropriateness for implementation into practice. However, the nutritional status of women of child-bearing age, particularly those who may be 'at risk', is a broader issue which needs further study. There is a need to focus both research effort and interventions upstream in an attempt to ensure that women arrive at pregnancy ready to meet the nutritional demands of gestation and ensure adequate foetal growth. Once again, this is a matter of high priority for public health and for the stated priority of ensuring a healthy start in life for all children.

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APPENDIX 1

Search strategy

1. meta.ab.
2. synthesis.ab.
3. literature.ab.
4. randomized.hw.
5. published.ab.
6. meta-analysis.pt.
7. extraction.ab.
8. trials.hw.
9. controlled.hw.
10. medline.ab.
11. selection.ab.
12. sources.ab.
13. trials.ab.
14. review.ab.
15. review.pt.
16. articles.ab.
17. reviewed.ab.
18. english.ab.
19. language.ab.
20. comment.pt.
21. letter.pt.
22. editorial.pt.
23. animal/
24. human/
25. 23 not (23 and 24)
26. exp birth weight/ or exp infant, low birth weight/ or exp infant, very low birth weight/ or exp infant, small for gestational age/ or birth weight.tw.
27. exp nutrition/ or exp nutritional support/ or exp dietary supplements/ or exp fetal growth retardation/ or nutrit\$.tw.
28. 26 or 27
29. exp pregnancy/ or exp pregnancy, high risk/ or exp pregnancy outcome/ or exp prenatal care/ or exp perinatal care/ or pregnancy.tw. or prenatal.tw.
30. 28 and 29
31. 30 not (20 or 21 or 22 or 25)
32. or/1-19
33. 31 and 32
34. limit 33 to yr=1996-2001
35. limit 34 to (human and english language) [Limit not valid in: CINAHL; records were retained]
36. exp pregnancy complications/ or exp pregnancy rate/ or exp pregnancy multiple/ or exp pregnancy, unwanted/ or exp obesity/ or exp developing countries/
37. 35 not 36
38. exp virus diseases/
39. 37 not 38

40. exp cesarean section/ or exp reproduction techniques/ or exp obstetric surgical procedures/ or exp tropanes/ or exp insemination/ or exp ovum implantation/
41. 39 not 40
42. exp breast feeding/
43. 41 not 42

Low birth weight and inequalities

1. meta.ab.
2. synthesis.ab.
3. literature.ab.
4. randomized.hw.
5. published.ab.
6. meta-analysis.pt.
7. extraction.ab.
8. trials.hw.
9. controlled.hw.
10. medline.ab.
11. selection.ab.
12. sources.ab.
13. trials.ab.
14. review.ab.
15. review.pt.
16. articles.ab.
17. reviewed.ab.
18. english.ab.
19. language.ab.
20. comment.pt.
21. letter.pt.
22. editorial.pt.
23. animal/
24. human/
25. 23 not (23 and 24)
26. exp infant, low birth weight/ or exp infant, very low birth weight/ or exp birth weight/ or exp pregnancy outcome/ or exp pregnancy, high risk/
27. exp social conditions/ or exp social class/ or exp social environment/ or exp community networks/ or exp social support/ or exp social isolation/ or exp social alienation/ or exp socioeconomic factors/ or exp poverty/ or exp social welfare/
28. 26 and 27
29. 28 not (20 or 21 or 22 or 25)
30. or/1-19
31. 29 and 30
32. limit 31 to yr=1990-2001
33. limit 32 to (human and english language)

APPENDIX 2

HDA Evidence Base – critical appraisal tool

Authors: _____

Title: _____

Source: _____

Relevance to topic			
Does this paper address your topic area?	Yes	No	Unsure
Circle the type of paper:			
• Systematic review			
• Meta-analysis			
• Synthesis			
• Literature review			
• Other review (please specify)			
Does it address (circle as appropriate)?			
• Effectiveness (interventions and treatments)			
• Causation			
• Monitoring and surveillance trends			
• Cost			
• Other (please specify)			
Transparency			
Does the paper have a clearly focused aim or research question?	Yes	No	Unsure
Consider whether the following are discussed:			
• The population studied	Yes	No	Unsure
• The interventions given	Yes	No	Unsure
• The outcomes considered	Yes	No	Unsure
• Inequalities	Yes	No	Unsure
Systematicity			
Do the reviewers try to identify all relevant English language studies?	Yes	No	Unsure
Consider whether details are given for:			
• Databases searched	Yes	No	Unsure
• Years searched	Yes	No	Unsure
• References followed up	Yes	No	Unsure
• Experts consulted	Yes	No	Unsure
• Grey literature searched	Yes	No	Unsure
• Search terms specified	Yes	No	Unsure
• Inclusion criteria described	Yes	No	Unsure
Is it worth continuing?	Yes	No	
Why/why not?			

Quality			
Do the authors address the quality (rigour) of the included studies? Consider whether the following are used:	Yes	No	Unsure
• A rating system	Yes	No	Unsure
• More than one assessor	Yes	No	Unsure
If study results have been combined, was it reasonable to do so? Consider whether the following are true:	Yes	No	Unsure
• Are the results of included studies clearly displayed?	Yes	No	Unsure
• Are the studies addressing similar research questions?	Yes	No	Unsure
• Are the studies sufficiently similar in design?	Yes	No	Unsure
• Are the results similar from study to study (test of heterogeneity)?	Yes	No	Unsure
• Are the reasons for any variation in the results discussed?	Yes	No	Unsure
What is the overall finding of the review? Consider: • How the results are expressed (numeric – relative risks, etc) • Whether the results could be due to chance (p-values and confidence intervals)			
Are sufficient data from individual studies included to mediate between data and interpretation/conclusions?	Yes	No	Unsure
Does this paper cover all appropriate interventions and approaches for this field (within the aims of the study)? If no, what?	Yes	No	Unsure
Relevance to UK			
Can the results be applied/are generalisable to a UK population/population group?	Yes	No	Unsure
• Are there cultural differences from the UK?	Yes	No	Unsure
• Are there differences in healthcare provision with the UK?	Yes	No	Unsure
• Is the paper focused on a particular target group (age, sex, population sub-group etc)?	Yes	No	Unsure
Accept for inclusion onto HDA Evidence Base?	Yes	No	Refer to third party
Additional comments			

Notes