BACKGROUND

Description of the condition

Pregnancy requires an increased intake of macronutrient and micronutrients for maternal and fetal needs, and malnourishment or inadequate dietary intake during pregnancy can lead to adverse perinatal outcomes. Observational studies (IOM 1990; Kramer 1987; Rush 2001) have indicated that both gestational weight gain and energy intake are strongly and positively associated with fetal growth, and possibly associated with a reduced risk of preterm birth. Moreover, these associations are stronger in undernourished women, i.e. those with low pre-pregnancy body mass index (BMI) (Ota 2011). Fetal development complications, such as low birthweight (LBW) and infants born small-for-gestational age, are associated with increases in perinatal mortality and morbidities (Ashworth 1998; Kramer 1987). Globally, it is estimated that more than approximately 20 million low birthweight infants are born each year, and more than 95% of these babies are born in developing countries (Unicef-WHO 2004). The effects of poor maternal nutrition on both immediate birth outcomes and longer term health has been well described in many epidemiological studies, including the effects from the Dutch winter famine of 1944 to 1945 (Stein 1975). Recognised longer-term health risks associated with poor infant growth include type 2 diabetes, hypertension, cardiovascular disease and obesity (Barker 1998; Barker 2002; Eriksson 2001).

Description of the interventions and how the interventions might work

Undernourished maternal nutritional status at conception and inadequate maternal nutritional status during pregnancy can result adverse perinatal outcomes (Viswanathan 2008). Dietary advice to pregnant women and balanced protein energy supplementation aim to achieve appropriate energy intakes lead to increase in maternal weight gain during pregnancy and fetal growth (de Onis 1998; Kulier 1998; Viller 1998). Protein generally comprises about 10% to 15% of dietary energy (Garlick 2000). Balanced protein energy supplementation (i.e. supplements in which protein provides less than 25% of the total energy content) has been shown to have significant positive impacts on maternal and perinatal birth outcomes, such as reductions in the incidences of preterm birth (Viller 1998), stillbirth (Imdad 2011) and intrauterine growth restriction (de Onis 1998). Furthermore, non-randomised trials have reported beneficial effects on fetal growth (Lechtig 1975; Prentice 1983), although the evidence from properly randomised trials suggests more modest benefits (Rush 1989; Rush 2001). On the other hand, data from severe dietary carbohydrate restriction with very high animal protein intake was counselled as part of routine antenatal care in a moderately affluent area suggest that high-protein dietary supplementation may have depressed birthweight by 400 g or more (Grieve 1979: Rush 1989). Isocaloric protein supplementation denotes a supplement, in which the protein content is 'balanced', i.e. provides less than 25% of its total energy content, but the protein replaced an equal quantity of non-protein energy in the control group. The observational findings reported for a non-randomised trial in Guatemala (Lechtig 1975) also suggest that protein supplementation is unlikely to benefit pregnant women or their infants.

Why it is important to do this review

Reliable high-quality information is required about the benefits and harms of energy/protein supplementation during pregnancy both for the woman and her infant. This review updates the review by one additional trial (Huybregts 2009), in order to aid clinical decisions and health policy-making.

OBJECTIVES

To assess the benefits and harms of dietary advice, supplementation or restriction on health outcomes for women and their infants. More specifically, the purpose of this review was to evaluate the five items listed below.

1. Effects of advising pregnant women to increase their energy and protein intakes on gestational weight gain and outcomes of pregnancy, including fetal growth, gestational duration, and maternal and fetal/infant morbidity and mortality.

2. Effects of balanced energy and protein supplements during pregnancy on gestational weight gain and outcomes of pregnancy.

3. Effects of high-protein nutritional supplements during pregnancy on gestational weight gain and outcomes of pregnancy.

4. Effects of isocaloric protein supplements (i.e. where the protein replaces an equal quantity of non-protein energy) during pregnancy on gestational weight gain and outcomes of pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials with randomisation at either individual or cluster level. We did not include quasi-randomised trials or cross-over trials.

For assessing dietary advice to increase energy and protein intakes: randomised controlled trials of such advice, whether administered on a one-to-one basis or to groups of women.

For assessing dietary supplementation: randomised controlled trials of energy and protein supplementation, with or without placebo.

Types of participants

All pregnant women with no systematic illness.

Types of interventions

Specific advice to increase dietary energy and protein intakes, energy and protein supplementation. The types of supplements included those that were 'balanced' energy and protein supplements (i.e. an energy supplement in which less than 25% of the energy is from protein), high-protein supplements (i.e. an energy supplement in which more than 25% of the energy is from protein), and isocaloric protein supplements (i.e. a supplement in which the protein content is 'balanced', i.e. provides less than 25% of total energy content, but the protein replaced an equal quantity of non-protein energy in the control group).

Types of outcome measures

Primary outcomes

- Perinatal mortality (defined by trialists)
- Stillbirth (death after 20 weeks' gestation and before birth)
- Neonatal death (death of a live infant within the first 28 days of life)

Secondary outcomes

Maternal outcomes

- Pre-eclampsia (defined by trialists)
- Energy intake (kcal/day)
- Protein intake (g/day)
- Gestational weight gain (kg)
- Duration of labour (hours)
- Mode of birth
- Number of antenatal hospital admissions
- Exclusive breast feeding at six months (defined by trialists)

Fetal/infant outcomes

- Birthweight (g)
- Small-for-gestational weight (defined by trialists)
- Low birthweight (less than 2500 g)
- Macrosomia (birthweight $\geq$ 4 kg and birth injury
- Birth length (cm)
- Birth head circumference (cm)
- Neurological development
- Preterm birth (prior to 37 weeks' gestation)
- Respiratory distress syndrome
- Admission to neonatal intensive care unit
- Chronic lung disease
- Periventricular leukomalacia
- Intraventricular haemorrhage
- Necrotising enterocolitis
- Retinopathy of prematurity
- Child growth (weight, height, head circumference, BMI)

Child outcomes

- Child growth (weight, height, head circumference, BMI)
- Neurological development

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (22 July 2011). We updated this search on 12 July 2012 and added the results to Studies awaiting classification.

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search

Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We contacted authors for additional data.
We did not apply any language restrictions.

Data collection and analysis

For the methods used when assessing the trials identified in the previous version of this review, *see* Appendix 1.
For this update, we used the following methods when assessing the trials identified by the updated search.

Selection of studies

Review authors Erika Ota (EO) and Ruoyan Tobe-Gai (RT) independently assessed all the potential studies we identified as a result of the updated search strategy for inclusion and resolved any disagreements through discussion or, if required, through consultation with Rintaro Mori (RM).

Data extraction and management

For eligible studies, EO and RT extracted the data independently and entered them into Review Manager software (RevMan 2011). We resolved any discrepancies through discussion or, if required, through consultation with RM. Data were checked for accuracy.
When information regarding any of the above was unclear, we attempted to contact the authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (EO and RT) independently assessed risk of bias for the one new study included in this update (Huybregts 2009) using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved discrepancies through discussion.
EO, RM and RT independently re-assessed the risk of bias for additional columns newly required for all the studies already included in the previous version with respect to changes in the methods (Higgins 2011).

(1) Sequence generation (checking for possible selection bias

For each included study, we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
We assessed the methods as indicated below:

- low risk of bias: any truly random process (e.g. random number table; computer random number generator);
- high risk of bias: any non-random process (e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

For each included study, we described the method used to conceal the allocation sequence in sufficient detail and determined whether the intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment.
We assessed the methods as indicated below:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (e.g. open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3) Blinding of participants, personnel and outcome assessment (checking for possible performance bias and detection bias)

For each included study, we described the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. Blinding was assessed separately for different outcomes or classes of outcomes.
We assessed the methods as indicated below:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel;
- low, high or unclear risk of bias for outcome assessment.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

For each included study, and each outcome or class of outcomes, we described the completeness of the data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses that we undertook.
We assessed methods as indicated below:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);

- unclear risk of bias.

(5) Selective reporting bias

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as indicated below:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review had been reported);
- high risk of bias (where not all of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and could not be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias caused by problems not covered by section (1) to (5) above)

For each included study, we described any important concerns we have about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias as indicated below:

- low risk of other bias;
- high risk of other bias;
- unclear risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to points (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented the results as the summary risk ratio with the 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if the outcomes were measured in the same way between trials. If necessary, we planned to use the standardised mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

Cluster-randomised trials

We included cluster-randomised trials in the analyses along with individually-randomised trials. We adjusted their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using an estimate of the intra-cluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we used ICCs from other sources, we reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. When we wanted to identify both cluster-randomised trials and individually-randomised trials, we planned to synthesise the relevant information. We would have considered it reasonable to combine the results from both if there was little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit was considered to be unlikely. Two of the trials (Ceesay 1997; Kafatos 1989) gave no published or unpublished data on the outcome-specific ICC. Therefore, we assumed a value of 0.01 and adjusted the corresponding sample sizes according to the design effect, i.e. by dividing the crude (individual) sample sizes by 1+ (m -1)r, where m is the average cluster size and r is the ICC (assumed to be 0.01). We conducted sensitivity analyses to investigate the effect of variation in the ICC (Figure 1; Figure 2).

Figure 1. Sensitivity analysis of the effect of clustering : Nutritional advice during pregnancy (1.7 preterm birth) Kafatos 1989

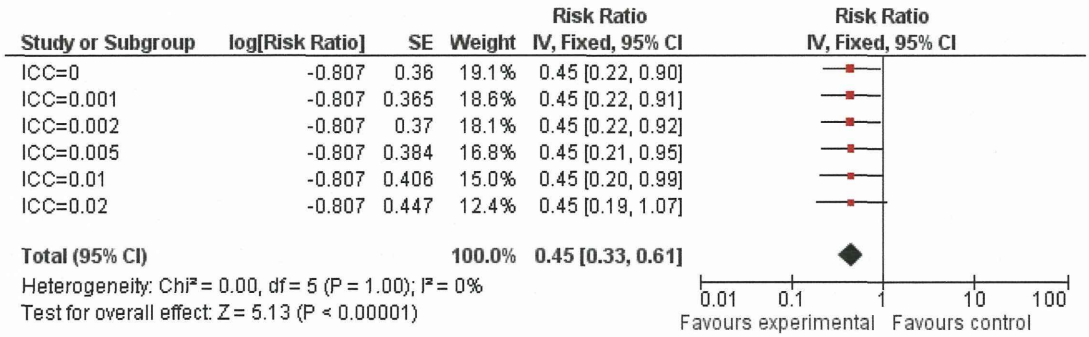
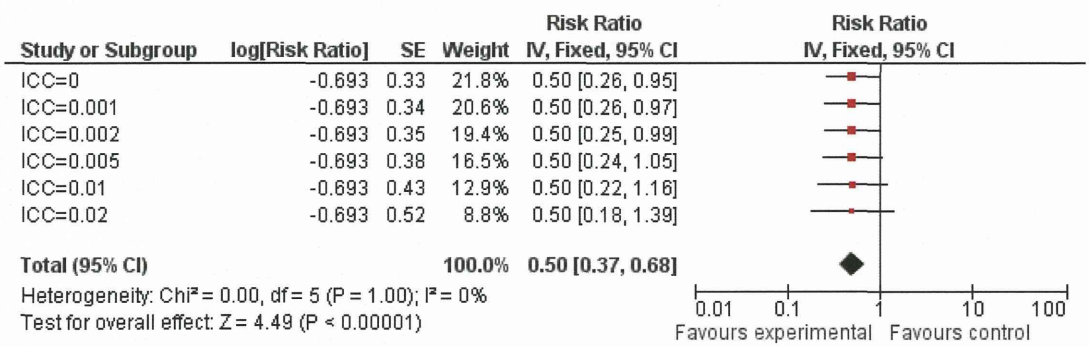


Figure 2. Sensitivity analysis of the effect of clustering : Balanced protein/energy supplementation in pregnancy (2.1 Stillbirth) Ceesay 1997



Cross-over trials

Cross-over trials were not considered in this review.

Dealing with missing data

For included studies, the levels of attrition were noted. The impact of including studies with high levels of missing data in the overall assessment of the treatment effect was explored using a sensitivity analysis.

All outcomes analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses. The denominator for each outcome in each trial was the randomised number minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed the statistical heterogeneity in each meta-analysis using T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the I^2 was greater than 30% and either T^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

If there were 10 or more studies in the meta-analysis, we investigated the reporting biases (such as publication bias) using funnel plots. We assessed the funnel plot asymmetry visually, and used formal tests for funnel plot asymmetry. For continuous outcomes, we used the test proposed by Egger 1997, and for dichotomous outcomes, we used the test proposed by Harbord 2006. If asym-

metry was detected in any of these tests or was suggested by a visual assessment, we performed exploratory analyses to investigate this.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan 2011). We used a fixed-effect inverse variance meta-analysis for combining data where trials were examining the same intervention, and the trials' populations and methods were judged to be sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used a random-effects meta-analysis to produce an overall summary when an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. Where the average treatment effect was not clinically meaningful, we did not combine trials.

When we performed random-effects analyses, the results were presented as the average treatment effects with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

When we identified substantial heterogeneity, we investigated it using subgroup analyses and sensitivity analyses. We considered whether an overall summary was meaningful, and if it was, we used a random-effects analysis to produce such a summary.

Since observational studies (IOM 1990; Kramer 1987) suggest a stronger association between gestational weight gain and fetal growth in women who were under-nourished before pregnancy, we stratified the analysis of the effects on mean birthweight into those trials in which the majority of women had low pre-pregnancy (or early pregnancy) weight (Ceesay 1997; Girija 1984; Kardjati 1988; Mora 1978; Rush 1980), and those in which the participants appeared adequately nourished (Elwood 1981; Ross 1985; Viegas 1982a). For the Taiwan trial (Blackwell 1973) and (Huybregts 2009; Viegas 1982b), within-trial stratification was possible, based on data contained in the published reports.

For fixed-effect inverse variance meta-analyses, we assessed differences between subgroups by interaction tests. For random-effects and fixed-effect meta-analyses using methods other than inverse variance, we assessed differences between subgroups by inspection of the subgroups' confidence intervals, in which non-overlapping confidence intervals indicated a statistically significant difference in the treatment effects between the subgroups.

Because growth varies with differences in sex (Onis 2007), it is desirable to compare growth between groups after adjusting for variations by sex. We conducted subgroup analysis on the children, separated by sexes for follow-up results of balanced protein and energy supplementation at the age of 11 to 17 years (height, weight, systolic blood pressure, diastolic blood pressure, BMI z-score, and body fat).

Sensitivity analysis

We carried out sensitivity analyses to explore the effects of fixed- or random-effects analyses for outcomes with statistical heterogeneity.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

Initially we examined 110 reports corresponding to 46 trials. Of these trials, 15 were included and 30 were excluded. One trial is ongoing (Moore 2011) with the results expected in 2013 (*see* Characteristics of ongoing studies). (Three reports from an updated search in July 2012 have been added to Studies awaiting classification.)

Included studies

We included 15 trials published between 1973 to 2009 that met the inclusion criteria. Most of the trials focused on assessing the effects of dietary advice, supplementation, or restriction on gestational weight gain, pre-eclampsia and/or pregnancy outcomes, or the development of the children. Four trials (Briley 2002; Hunt 1976; Kafatos 1989; Sweeney 1985) evaluated nutritional advice to increase energy and protein intake. Eleven trials (Blackwell 1973; Ceesay 1997; Elwood 1981; Girija 1984; Huybregts 2009; Kardjati 1988; Mora 1978; Ross 1985; Rush 1980; Viegas 1982a; Viegas 1982b) assessed the impact of balanced energy/protein supplementation. Only one trial assessed the effects of high-protein nutritional supplements (Rush 1980). Two trials (Viegas 1982a; Viegas 1982b) investigated the effects of isocaloric protein supplements. Seven trials were from high-income countries such as the USA and UK, and eight trials from low- and middle-income countries such as Ganbia, Taiwan, India, Burkina Faso, Greece, Indonesia, Colombia, South Africa. Four trials were conducted in an economically disadvantaged area including under-nourished populations; the other 11 trials included well-nourished populations. Interventions for nutritional advice included counselling or classes versus no interventions (three trials; Hunt 1976; Kafatos 1989; Sweeney 1985) and counselling versus home visits without

counselling (one trial; Briley 2002). Interventions for balanced energy and protein supplementation included supplementation versus control supplements (eight trials; Blackwell 1973; Huybregts 2009; Kardjati 1988; Mora 1978; Ross 1985; Rush 1980; Viegas 1982a; Viegas 1982b) and supplementation versus no intervention (three trials; Ceesay 1997; Elwood 1981; Girija 1984). Intervention for high-protein nutritional supplements included supplementation versus supplement containing vitamins/minerals (Rush 1980). Intervention for isocaloric-protein nutritional supplements included supplementation versus supplement of flavoured carbonated water containing iron and vitamin C (Viegas 1982a; Viegas 1982b).

For details of the included studies, *see* the Characteristics of included studies table.

Excluded studies

We excluded 30 trials. Of these trials, eight trials did not match the interventions in this review, nine involved participants who were outside the scope of the review, one did not have a control group, one trial's analysis was based on individual women despite randomising by village, and 11 trials did not involve randomisation, or the designs were outside the scope of the review.

For details of the excluded studies, *see* the Characteristics of excluded studies table.

Risk of bias in included studies

See Figure 3 and Figure 4.

Figure 3. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

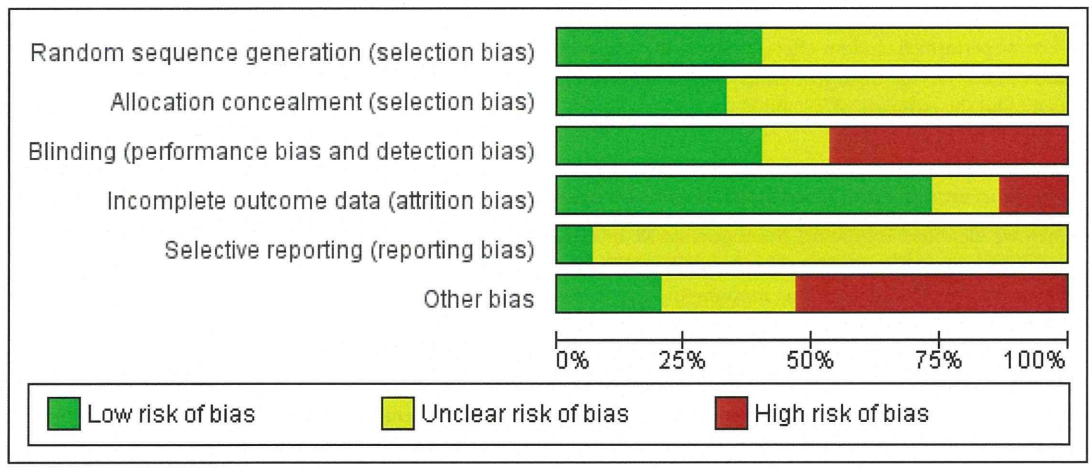
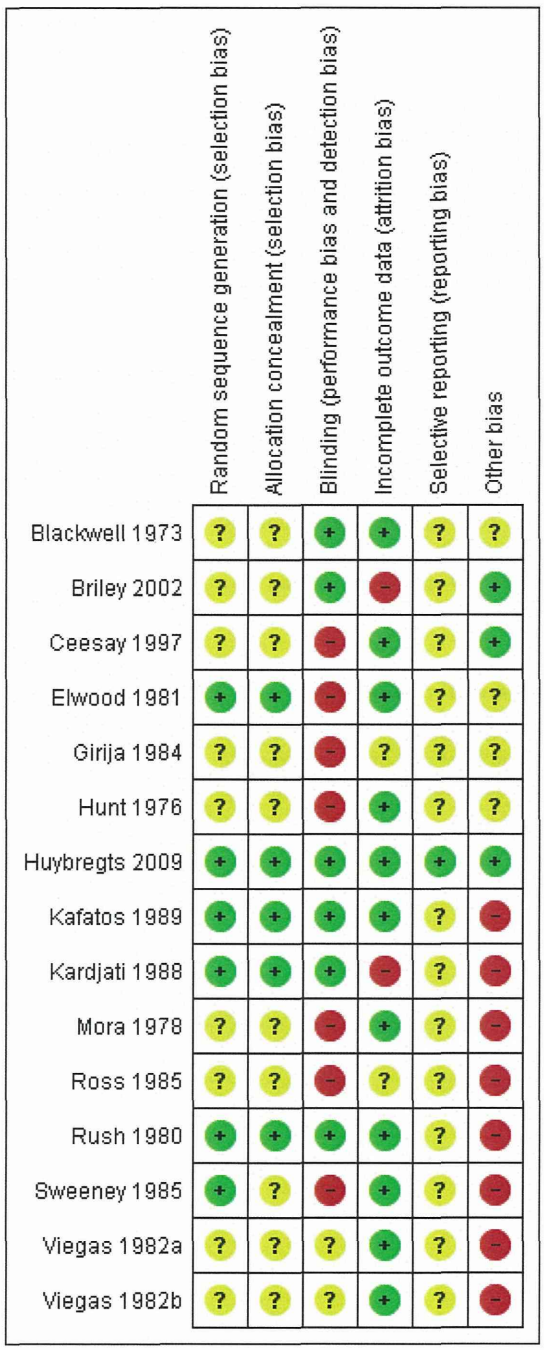


Figure 4. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation (selection bias)

Sequence generation

Six trials had a low risk of bias because of adequate randomisation of participants to the intervention groups (Elwood 1981; Huybregts 2009; Kafatos 1989; Kardjati 1988; Rush 1980; Sweeney 1985). For nine trials, risk of bias could not be adequately judged because no detailed information was provided about allocation sequence generation (Blackwell 1973; Briley 2002; Ceesay 1997; Girija 1984; Hunt 1976; Mora 1978; Ross 1985; Viegas 1982a; Viegas 1982b).

Allocation concealment

Five trials had a low risk of bias through the use of sequentially numbered, opaque, sealed envelopes or drug containers of identical appearance (Elwood 1981; Huybregts 2009; Kardjati 1988; Rush 1980; Sweeney 1985). Ten trials provided no information about allocation concealment (Blackwell 1973; Briley 2002; Ceesay 1997; Girija 1984; Hunt 1976; Kafatos 1989; Mora 1978; Ross 1985; Viegas 1982a; Viegas 1982b).

Blinding (performance bias and detection bias)

Six trials had a low risk of bias using single or double blinding, or used no blinding but reported outcomes and outcome measurements that were not likely to be influenced by the lack of blinding. Seven trials had a high risk of bias owing to a lack of blinding. Two trials could not be judged for the risk because no information was provided (Viegas 1982a; Viegas 1982b).

Incomplete outcome data (attrition bias)

Losses to follow-up ranged from 1.5% in Viegas 1982b to 25.9% in Briley 2002. Eleven trials had a low risk of bias, two trials had a high risk of bias and two trials were judged as unclear bias owing to insufficient information.

Selective reporting (reporting bias)

Fourteen trials were judged as unclear risk because the protocol was not available for judgment of this bias. Only one trial (Huybregts 2009) had a protocol and was judged as low risk for selective reporting.

Other potential sources of bias

Eight trials had a high risk of bias because no data were presented on compliance or substitution, and for other reasons. Three trials had a low risk of bias and four trials had insufficient information and were judged as unclear risk.

The funnel plots (Figure 5; Figure 6) did not show any publication bias.

Figure 5. Funnel plot of comparison: 2 Balanced protein/energy supplementation in pregnancy, outcome: 2.3 Birthweight (g).