(birth head circumference), and low quality (Stillbirth, neonatal death, preterm birth, infants born small-for-gestational age and protein intake) which includes two of the primary outcomes, to very low quality (birthweight) suggesting that the estimates were very uncertain. In the balanced protein and energy supplementation in pregnancy studies (Summary of findings 2), with significant reductions in stillbirth and infants born small-for-gestational age, and significant increase in birthweight were considered to be of moderate quality. Preterm birth was moderate quality. Neonatal death were of low quality and pre-eclampsia was of very low quality. In the high-protein supplementation in pregnancy studies (Summary of findings 3), the significant increase in infants born small-for-gestational age was of moderate quality in only one study (Rush 1980). In the isocaloric balanced protein supplementation in pregnancy studies (Summary of findings 4), the evidence was judged to be of very low quality (birthweight, weekly gestational weight gain) meaning that the estimates were very uncertain.

Potential biases in the review process

There were several potential biases in the review process. We made efforts to limit the bias in several ways: two review authors assessed the eligibility for inclusion and assessed the risks of bias independently. Although the authors' views varied, we decided to accept the final conclusions after extensive discussion and reaching a consensus. Carrying out reviews, however, may require a number of subjective judgements, and it is possible that a different review team may have reached different decisions regarding the assessments of eligibility and risks of bias. Feedback from readers will serve to improve the next review update.

Agreements and disagreements with other studies or reviews

We have included only randomised controlled trials (RCTs) and excluded the quasi-RCTs previously included in the review (Kramer 2003). The new findings of this review are that balanced energy and protein supplementation was associated with significant increases in mean birthweight, while the other major findings are consistent with those of the previous Cochrane Review (Kramer 2003). Prenatal supplementation with multi-micronutrients was associated with a significantly reduced risk of low-birthweight infants and with improved birthweight when compared with iron-folic acid supplementation, although there was no effect on the risk of preterm birth or small-for gestational-age infants (Shah 2009). Researchers should aim to include only those women in trials to increase energy and protein intake who have the potential to benefit. Observational data suggest women who are overweight or obese or who exceed their daily energy and protein requirements during pregnancy are at increased risk of adverse pregnancy outcomes including: stillbirth and large-for-gestational age and macrosomia (birthweight $\geq$ 4 kg) (Chen 2009; Heslehurst 2008; Thangaratinam 2012), therefore, the effect of increasing protein and energy intakes could have opposite effects on different populations within the same trial if those included are not adequately defined and selected.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides encouraging evidence that nutritional advice to increase protein and energy intake and balanced energy and protein supplementation may reduce some perinatal adverse outcomes. The long-term effects are unclear and it seems likely that targeting undernourished women rather than the whole obstetric population would convey the most benefit. For most of the included trials in this review, the risk of bias was either unclear or high for at least one category examined, and the results of this review should therefore be interpreted with caution.

Nutritional advice appears to be effective in increasing pregnant women's protein intake, and increases fetal growth such as birth head circumference. The 54% relative reduction in preterm birth for nutritional advice in energy and protein compared with no nutritional counselling may be beneficial to pregnant women.

Balanced energy and protein supplementation appears to reduce the risks of stillbirth, although the biological mechanisms underlying these reductions remain unclear. Furthermore, balanced protein and energy intervention, as provided in most trials, results in significant increases in maternal weight gain and infant birthweight, and decreases the risk of infants born in small-for-gestational age. These effects do not seem to confer long-term benefits to the child in terms of growth, neurocognitive development, and adiposity or blood pressure. The available evidence is inadequate to evaluate the potential effects on preterm birth, neonatal death or maternal health.

Based on the available evidence, there is no justification for prescribing high-protein and isocaloric nutritional supplements to pregnant women, although the number of trials and women included are few.

Implications for research

High-quality randomised trials are needed that target those women who are nutritionally deprived or underweight with reduced energy intake; long-term follow-up is required.

Given the modest benefits in preterm delivery documented for balanced energy and protein advice during pregnancy, future randomised trials need to assess the effects on perinatal outcomes

such as stillbirth, neonatal death and birthweight. Effective interventions, such as the content and frequency of nutritional advice, need to be clarified.

Future energy and protein supplementation trials should focus their attention on outcomes other than fetal growth, especially in undernourished women and particularly on confirming the evidence of intervention on reduced risks of stillbirth and infants born small-for-gestational age. Such trials will require large sample sizes. Any future trials should also assess the effects on women, including duration of labour, caesarean section, macrosomia and postpartum weight retention.

The lack of evidence of benefit, coupled with the possibility of harm, suggests that future trials of high-protein supplementation, and isocaloric protein supplementation should not be considered.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team) and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Blackwell 1973

Methods	Interventions 'assigned randomly and blindly', but method not specified
Participants	Well-nourished rural Taiwanese women with 'marginal' diets (estimated daily energy intake is approximately 2000 kcal and protein intake <= 40 g for adult women in this area from preliminary food survey in 1965)
Interventions	Experimental: chocolate-flavoured liquid supplement given twice daily beginning after prior birth and continuing during index pregnancy; supplement contained 40 g protein and 800 kcal energy plus vitamins/minerals. Control: supplement containing vitamins and minerals only, but given at same times and for same duration
Outcomes	Gestational weight gain, preterm birth, birthweight, small-for-gestational age, length, head circumference, and IQ at age 5
Notes	1) Data presented on dietary substitution, but based on meal survey only. 2) High alleged net energy supplement not associated with significantly higher gestational weight gain. 3) Discrepancies in first-infant LBW rates in 1981 vs 1973 reports. 4) Significant correlation between birthweight and energy (and supplement) intake in controls only. 5) Supplementation continued until 15 months postpartum; data on maternal postpartum weight therefore, omitted from review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Although details are not described, it says the study participants were randomly assigned
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	Low risk	The 2 supplements were similar and no women were considered to be able to distinguish them
Incomplete outcome data (attrition bias) All outcomes	Low risk	506 out of 524 (96.5%) were with complete data for the analysis and this was not ITT

Blackwell 1973 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No description on this. Not mentioned on registered protocol
Other bias	Unclear risk	No data were provided for background characteristics.

Briley 2002

Methods	Randomisation method not reported.
Participants	27 low-income African-American women. Mean pre-pregnancy body mass index is within the normal range for both groups (intervention, 24.7±3.4, control, 23.2 ±4.1 kg/m^2)
Interventions	Experimental: minimum of 6 individualised in-home nutrition assessment and counselling visits. Control: 2 home visits without counselling.
Outcomes	Energy intake, gestational weight gain, birthweight, and preterm birth
Notes	1) 7 of 27 randomised women dropped out and not included in analysis. 2) Neither participants nor observers apparently blind to allocation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Women were randomly assigned, though no detailed methods on randomisation were described
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Counselling group is evident and interventions could not be blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	7 women dropped out of 27 women (74.1%) and no ITT.
Selective reporting (reporting bias)	Unclear risk	Uncertain, as if the protocol was registered, etc. was not described
Other bias	Low risk	There was no significant difference in demographic background between the groups

Ceesay 1997

Methods	Cluster randomisation by village "using a stratified design according to village size", but no details provided on method of random allocation or concealment
Participants	Rural Gambian women from 28 villages with "chronically" marginal nutrition. Undernutrition more pronounced from June to October (the 'hungry' season involving low food supply and heavy agricultural work) than from November to May (the dry harvest season with adequate food supply and less strenuous work).The mean maternal body mass index measured after delivery was 20.7± 2.3 kg/m^2 in the control group and 21.3 ± 2.8 kg/m^2 in the intervention group.
Interventions	Experimental villages: 2 supplement biscuits containing roasted groundnuts, rice flour, sugar, and groundnut oil (4250 kJ (1017 kcal) energy, 22 g protein, 56 g fat, 47 mg calcium, and 1.8 mg iron)] consumed daily in presence of birth attendants. Supplementation began at 20 weeks' gestation. Control villages: no supplement.
Outcomes	Gestational weight gain, GA, birthweight, birth length, head circumference, stillbirth, and neonatal death
Notes	1) Randomisation by cluster (village), but effects reported for individual births, based on multilevel (3-stage random-effects) modelling with separate error terms for village, mother, and (for mothers with more than 1 pregnancy during study) baby. 2) Results reported both overall and stratified by season (hungry vs harvest), but this review based on overall data. Note that definitions of seasons are not entirely consistent with previous (non-randomised) studies from this group and were chosen because 'post hoc analysis indicated that this selection yielded the greatest discrimination between hungry and harvest season effects'. 3) Many outcome analyses are based on individual women and therefore, do not account for the intra-class correlation among women living in the same village. Sample sizes in these outcomes have therefore, been adjusted downward to the nearest integer by dividing by 1+(m-1)r, where m is the average number of women per village and r = 0. 01 is the (assumed) intra-class correlation co-efficient 4) Data on LBW used in analysis of infant born small-for-gestational age. 5) Number of intervention and control participants reversed in column headings of Table 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Villages were randomly assigned, but no details provided on method of random allocation
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of allocation concealment is not described
Blinding (performance bias and detection bias) All outcomes	High risk	The supplement biscuits provided in intervention group only. Intervention was evi-

Ceesay 1997 *(Continued)*

		dent
Incomplete outcome data (attrition bias) All outcomes	Low risk	Over 95% agreed and remained in the trial throughout,The analysis presented here covers 2047 normal singleton live births from 1460 different women who delivered during October 1989 to October 1994
Selective reporting (reporting bias)	Unclear risk	Not clear if the protocol was registered prior to the study.
Other bias	Low risk	Similar between the groups and multilevel multiple regression was employed

Elwood 1981

Methods	Randomisation based on random numbers with sealed envelopes.
Participants	1251 pregnant Welsh women in 2 small towns recruited at time of first reporting of pregnancy in South Wales, UK. No information available for pregnant women's pre-pregnancy BMI
Interventions	Experimental: free tokens worth ½ pint milk each. Control: no intervention.
Outcomes	GA, preterm birth, birthweight, LBW, length, and head circumference
Notes	1) 24% of women lost to follow-up, with evidence of higher losses in control group. 2) No adjustment for higher percentage of smokers in control group. 3) Trial also includes postnatal milk supplement (tokens) in children; all data on postnatal growth in children therefore, omitted from review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation based on random numbers with sealed envelopes.
Allocation concealment (selection bias)	Low risk	Randomisation based on random numbers with sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	High risk	Allocation was evident.
Incomplete outcome data (attrition bias) All outcomes	Low risk	212 were loss of follow-up. 82% were analysed.

Elwood 1981 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Not enough information was provided.
Other bias	Unclear risk	Not enough information was provided.

Girija 1984

Methods	Randomly allocated.
Participants	20 poor Indian women in last trimester. Pregnant women's weight at last trimester was approximately 47 kg in both intervention group and control group
Interventions	Experimental: supplement containing 50 g sesame cake, 40 g jaggery, and 10 g oil (417 kcal energy and 30 g protein). Control: normal (unsupplemented) diet.
Outcomes	Gestational weight gain, birthweight, length, head circumference, breast milk output, and weight, length, and head circumference, through 3 months of age
Notes	1) Large losses to follow-up for breast milk output. 2) No SDs reported on postnatal anthropometric outcomes, so data not included in review. 3) No data reported on compliance or dietary substitution. 4) Energy and protein intakes appear higher before supplementation, even in supplemented group. 5) Mean GA (between 36 and 37 weeks in both groups) is incompatible with reported rates of preterm birth (0 of 10 in both groups), so data on preterm birth are omitted from review

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The participants were randomly assigned though no other details were provided
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	High risk	The allocation was evident.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information was given.
Selective reporting (reporting bias)	Unclear risk	No enough information was given.

Girija 1984 *(Continued)*

Other bias	Unclear risk	No description on demographic characteristics and others.

Hunt 1976

Methods	Method of randomisation not reported.
Participants	344 Spanish-speaking women with first prenatal clinic visit <= 21 weeks' gestation in Los Angeles. Pre-pregnancy self-report weight for intervention group was 127 ± 19 lb, and control group was 126 ± 23 lb
Interventions	Experimental: nutrition classes (average of 3 per woman). Control: no classes
Outcomes	Protein and energy intakes; no data on gestational weight gain or pregnancy outcome
Notes	1) 65 women excluded or lost (not interviewed) post-randomisation. 2) Possible 'contamination' via contact between women in 2 groups. 3) No blinding.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The women were randomly assigned to a control or treatment group. Method of randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information, the method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding, possible 'Contamination' via contact between women in the groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	279 (81%) women were followed. Reasons for missing outcome data balanced in numbers across groups
Selective reporting (reporting bias)	Unclear risk	No protocol, insufficient information to permit judgement.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exist

Huybregts 2009

Methods	A non-blinded, individually randomised controlled trial. A randomisation scheme was generated by a computer program in permuted blocks of 4. Randomisation numbers were sealed in opaque envelopes by administrative staff
Participants	1296 Pregnant women in 2 villages In rural Burkina Faso. BMI at entry of the trial for intervention group was 20.8 ± 2.2 kg/m^2, and control group was 21.0 ± 2.2 kg/m^2.
Interventions	Intervention: prenatal multiple micronutrient (MMN) + fortified food supplement (FFS) Control: MMN
Outcomes	Anthropometric measures at birth, LBW, infant born small-for-gestational age, LGA, GA, preterm
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A randomisation scheme was generated by a computer program in permuted blocks of 4. Randomisation numbers were sealed in opaque envelopes by administrative staff
Allocation concealment (selection bias)	Low risk	Sequentially numbered, opaque, sealed envelopes.
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but care was taken to blind staff who performed the anthropometric measurements at delivery; measurement bias was therefore unlikely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis for 87% of the 1175 live singleton deliveries enrolled
Selective reporting (reporting bias)	Low risk	The trial was registered at clinical trials.gov as NCT00909974
Other bias	Low risk	The compliance was closely verified by using a community-based network of home visitors

Kafatos 1989

Methods	Randomisation of 20 clinics using computer-generated random numbers
Participants	568 pregnant women in rural area in Northern Greece < 27 weeks' gestation. Initial BMI was 23.10 ± 0.2 kg/m^2in intervention group, and 22.7 ± 0.2 kg/m^2 in control group.
Interventions	Experimental: nutrition counselling to improve 'quality' of diet ('high nutrient value'). Control: no counselling
Outcomes	Energy and protein intake, serum vitamin and mineral levels, gestational weight gain, birthweight, birth length and head circumference, GA, LBW, infant born small-for-gestational age, preterm birth, stillbirth, and neonatal death
Notes	1) Analysis based on individual women, rather than clinic. To account for the intra-class correlation among women attending the same clinic, sample sizes have been adjusted downward to the nearest integer by dividing by 1+(m-1)r, where m is the average number of women per clinic (30.0 intervention and 26.8 control) and r = 0.01 is the (assumed) intra-class correlation. 2) Dietary intake unblinded, and energy intake higher in experimental group prior to intervention. 3) Inconsistent results: lower preterm rate, yet no difference in mean GA; higher head and chest circumferences but no difference in birthweight. 4) Discrepancies in sample sizes for different outcomes, even birthweight vs LBW rate. 5) SEM of GA in intervention (experimental) group assumed to be 0.10, not the 0.01 shown in Table 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A cluster randomisation of 20 clinics using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Randomisation by clinic using computer-generated random numbers, clinic enrolled all women to minimise selection bias for allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding but the possible contamination effects of the educational program in that women from the same village or neighbourhood attending the same clinic would be enrolled in the same group
Incomplete outcome data (attrition bias) All outcomes	Low risk	For dietary records, Intervention group 216 (86.7%), control group 180(94.2%) were followed up after allocation
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement.

Kafatos 1989 *(Continued)*

Other bias	High risk	Energy intake higher in experimental group prior to intervention

Kardjati 1988

Methods	"Blind" randomisation based on household numbers, with use of random-numbers table
Participants	747 women in 3 villages in rural East Java (an area known to be 'nutritionally vulnerable' (Kardjati 1983) at 26-28 weeks' gestation. Total mean ± SD pre-pregnant BMI was 18. 7 ± 2.0 kg/m^2.
Interventions	Experimental: supplement containing a dry powder (50% fat, 10% casein, and 40% glucose) providing 465 kcal energy and 7.1 g protein ('high energy'). Control: supplement containing 52 kcal energy and 6.2 g protein ('low energy')
Outcomes	Gestational weight gain, birthweight, and breast milk output
Notes	1) Although data on birthweight were not analysed according to ITT, they are included in this review because birthweight was similar in the 2 study groups and in non-compliers (both groups combined). 2) Data on gestational weight gain are based on the combined results in all 3 compliance strata but are missing for approximately one-third of study participants. 3) Data on breast milk output based on a selection of 50% of 'randomly'-selected study participants (only 10% of total study sample). Data excluded on 16 'uncooperative' or 'repeatedly absent' participants. 4) Data on postnatal infant growth reported in Kusin 1992 have been excluded from review, because poor compliers were excluded from the analysis (i.e., not based on ITT)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The household numbers were the basis for allocation using random number tables
Allocation concealment (selection bias)	Low risk	Using random number tables.
Blinding (performance bias and detection bias) All outcomes	Low risk	While the study was not blind, the randomisation was, since the characteristics of the pregnant women cannot be inferred from the household numbers
Incomplete outcome data (attrition bias) All outcomes	High risk	Birthweight was recorded in 419 liveborn singletons (87%). Gestational weight gain is missing for approximately one-third of study participants

Kardjati 1988 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Protocol not available.
Other bias	High risk	The absence of a difference in mean birthweight between the HE and LE groups as a whole may be attributed to a masking effect of the better home diet in the experimental period

Mora 1978

Methods	Allocation method not reported.
Participants	456 poor first-or second-trimester women from Bogota slum for whom at least 50% of previous children had weight-for-height < 85% of Colombian standard. No information about maternal anthropometry (weight or BMI) provided
Interventions	Experimental: supplement containing 60 g dried skim milk, 150 g enriched bread, and 20 g vegetable oil (856 kcal energy and 38.4 g protein) beginning in third trimester. Control: normal (unsupplemented) diet.
Outcomes	Pre-eclampsia, GA, preterm birth, birthweight, LBW, stillbirth, perinatal mortality, neonatal mortality
Notes	1) Compliance assessed but data not presented. 2) Substitution assessed by single 24-hour recall 8 weeks after starting supplement. 3) Preterm birth rate not increased, but higher mortality reported among those born preterm. 4) Data on term LBW used in analysis of infant born small-for-gestational age

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly assigned either to a supplemented or an unsupplemented group
Allocation concealment (selection bias)	Unclear risk	Allocation method not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Supplemented group (186/226, 82.3%), unsupplemented group(173/230, 75.2%) were followed. Total sample and subsample in table2 showed no significant difference in characteristics

Mora 1978 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol available, insufficient information to judge this
Other bias	High risk	Compliance not mentioned.

Ross 1985

Methods	Allocation method not reported.
Participants	127 Black South African women < 20 weeks' gestation.Study women averaged > 70 kg at 20 weeks
Interventions	Experimental: supplement containing 700-800 kcal energy and 36-44 g protein. 2 types of supplements were given: a high-bulk mixture of beans and maize, given as mush with added vitamins, and a low-bulk porridge containing dried skimmed milk, maize, flour, vitamins, and minerals; the high- and low-bulk groups are combined in the experimental group for this review. Control: placebo pills (zinc-supplemented group is excluded from review)
Outcomes	Gestational weight gain (after 20 weeks), GA, and birthweight
Notes	1) Higher gestational weight gain in control group argues against causal association with birthweight. 2) No data presented on compliance or substitution. 3) Number of women originally randomised not reported ('90% continued ... to delivery'). 4) Original sample size not given nor its justification.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	127 Zuru women were randomly assigned to 4 groups.
Allocation concealment (selection bias)	Unclear risk	Allocation method not reported.
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of women originally randomised not reported, or no missing case
Selective reporting (reporting bias)	Unclear risk	Protocol is not available.
Other bias	High risk	No data presented on compliance or substitution.