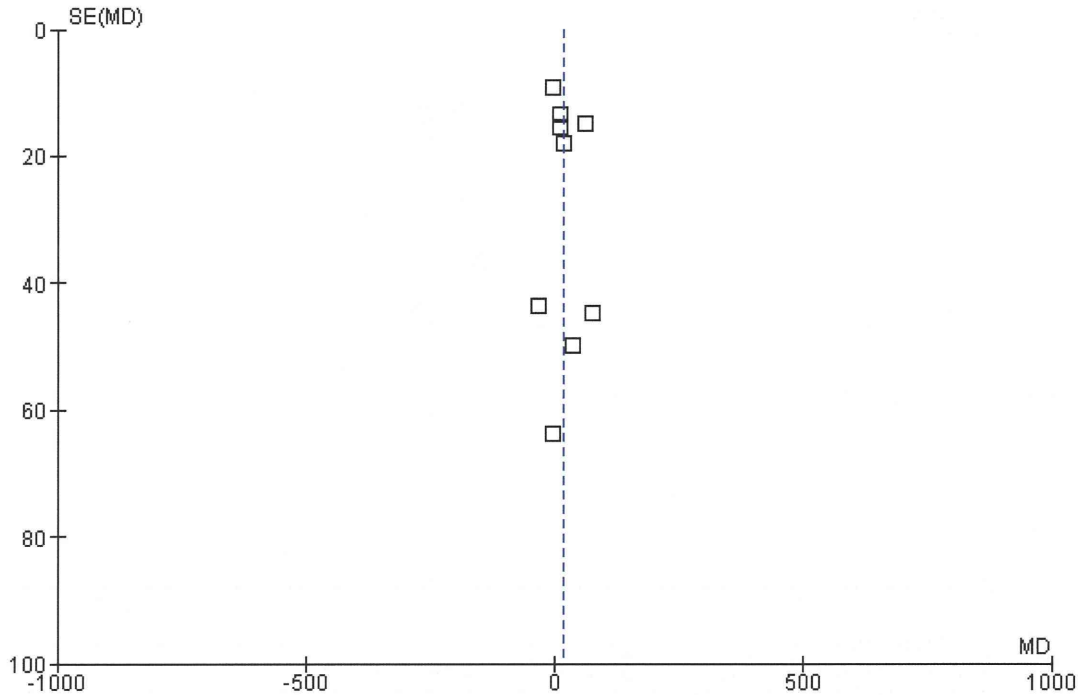
**Figure 6. Funnel plot of comparison: 2 Balanced protein/energy supplementation in pregnancy, outcome: 2.9 Weekly gestational weight gain (g/week).**




## Effects of interventions

See: **Summary of findings for the main comparison** Nutritional advice compared to no counselling or advice during pregnancy for perinatal outcomes; **Summary of findings 2** Balanced protein and energy supplementation compared to control or no intervention in pregnancy for perinatal and maternal outcomes; **Summary of findings 3** High protein supplementation in pregnancy and perinatal outcomes; **Summary of findings 4** Isocaloric balanced protein supplementation in pregnancy and outcomes

### Nutritional advice to increase energy and protein intakes

Four trials of nutritional advice, involving 790 women, were included. For the primary outcomes, there was no significant effect on stillbirth (risk ratio (RR) 0.37, 95% confidence interval (CI) 0.07 to 1.90; one trial, 431 women- Analysis 1.1) or neonatal death (RR 1.28, 95% CI 0.35 to 4.72; one trial, 448 women- Analysis 1.2 ). There was no significant effects on the outcomes of birthweight (Analysis 1.3), birth length (Analysis 1.4), and small-for-gestational age (Analysis 1.6). Because the results of total gestational weight gain (Briley 2002; Kafatos 1989) were inconsistent and showed high heterogeneity we have not combined the studies in the analysis (no total shown in Analysis 1.11). Birth head circumference (cm) was significantly increased in the intervention group (mean difference (MD) 0.99 cm, 95% CI 0.43 to 1.55; one trial, 389 women - Analysis 1.5). The 'significant' reduction in preterm birth associated with advice (RR 0.46, 95% CI 0.21 to 0.98, P < 0.05; two trials, 449 women - Analysis 1.7) was not consistent with the total absence of effect on mean gestational age (MD -0.10 weeks, 95% CI -0.48 to 0.28; one trial, 399 women - Analysis 1.8). Sensitivity analyses (Figure 1) was conducted in using values of 0.01 for the ICC did not qualitatively change the relative risks for preterm in Kafatos 1989. Within the methodological limitations discussed above, advice to increase protein intake seems to be successful in achieving its goal (protein intake: MD +6.99 g/day, 95% CI 3.02 to 10.97, P < 0.05; three trials, 632 women- Analysis 1.9), but there was no significant increase in energy intake (energy intake: MD +105.61 kcal/day, 95% CI -18.94 to 230.15, P = 0.10; three trials, 342 women - Analysis 1.10).

### Balanced energy/protein supplementation

Eleven trials, involving 5385 women, were included. Providing balanced energy and protein supplementation significantly reduced the risk of stillbirth (RR 0.62, 95% CI 0.40 to 0.98; five trials, 3408 women - Analysis 2.1). Neonatal death was unaffected (RR 0.68, 95% 0.43 to 1.07; five trials, 3381 women - Analysis 2.2). Sensitivity analyses (Figure 2) for ICCs of 0.02 to 0 made little difference, using values of 0.01 for the ICC did not qualitatively change the relative risks for stillbirth in Ceesay 1997.

Supplementation was also associated with significant increases in mean birthweight (random-effects MD +40.96 g, 95% CI 4.66 to 77.26, $Tau^2$ = 1744, $I^2$ = 44%, P = 0.03; 11 trials, 5385 infants - Analysis 2.3 ). Although clinically small, birth length (cm) was statistically significantly increased (fixed-effect MD +0.16 cm, 95% CI 0.01 to 0.31; five trials, 3370 women - Analysis 2.4), while no significant difference was found for birth head circumference (Analysis 2.5). The incidence of small-for-gestational age birth was significantly reduced (RR 0.79, 95% CI 0.69 to 0.90, $I^2$ = 16%; seven trials, 4408 women - Analysis 2.6). There were no significant effects observed on preterm birth (Analysis 2.7), gestational age (week) (Analysis 2.8), or weekly gestational weight gain (g/week) (Analysis 2.9). The rather meagre data on pre-eclampsia did not suggest a reduction in risk with supplementation (RR 1.48, 95% CI 0.82 to 2.66; two trials, 463 women - Analysis 2.10).

Although postnatal follow-up was limited to a small number of trials, the enhancement of fetal growth observed in those trials was not reflected in larger size or improved neurocognitive development at one year. Bayley mental score at one year had no significant effect in one trial (Rush 1980; Analysis 2.11). The Taiwan trial (Blackwell 1973) detected no effect on Stanford-Binet IQ score at five years (Analysis 2.12), and weight at one year (Analysis 2.13). The data of the standard deviation of length at one year for Blackwell 1973 were not credible compared with the Rush 1980 study, we have omitted this trial from the analysis and only showed the data from Rush 1980 (Analysis 2.14). There was no significant effect on head circumference at one year from either the Taiwan (Blackwell 1973) or Harlem trials (Rush 1980) (Analysis 2.15).

Maternal outcomes other than weight gain were reported infrequently. Only one trial each reported results on other outcomes. The Bogota trial (Mora 1978) detected no significant reduction in duration of labour with supplementation (Analysis 2.16). The East Java trial (Kardjati 1988) found neither an increase in maternal weight at four weeks postpartum (Analysis 2.17).

Follow-up at 6.5 to 9.5 years of age for approximately 25% of the children randomised in Ceesay 1997 found no difference in immune function (delayed-hypersensitivity skin tests, antibody responses to pneumococcal and rabies vaccines, and salivary IgA concentration) between the intervention and control groups (data not shown in data and analysis table). Follow-up at 11 to 17 years of age for approximately two-thirds of the children who were still alive found no significant differences in height (Analysis 2.18), weight (Analysis 2.19), or systolic or diastolic blood pressure (Analysis 2.20; Analysis 2.21), but did find a small increase in the mean BMI z-score (MD +0.16, 95% CI +0.01 to +0.31; one trial, 855 children - Analysis 2.22) in the control group. However, the difference in BMI was in contrast with the absence of the effect on per cent body fat (Analysis 2.23).

### High-protein supplementation

Only one trial (Rush 1980), involving 1051 women, was included. For primary outcomes, the Harlem trial (Rush 1980) reported non-significant effects in stillbirth (RR 0.81, 95% CI 0.31 to 2.15; one trial, 529 women - Analysis 3.1) and neonatal death (RR 2.78, 95% CI 0.75 to 10.36; one trial, 529 women - Analysis 3.2) with high-protein supplementation. The only available trial (Rush 1980) provided the evidence of significant increases in infants born small-for-gestational age (RR 1.58, 95% CI 1.03 to 2.41, P = 0.04; one trial, 505 women - Analysis 3.3), although no significant effect for birthweight (Analysis 3.4) or preterm birth (Analysis 3.5).

High-protein supplementation had no effect on weekly gestational weight gain (MD +4.50 g/week, 95% CI -33.55 to +42.55; one trial, 486 women - Analysis 3.6). At one-year follow-up in the Harlem trial (Rush 1980), high-protein supplementation was not associated with detectable differences in weight (Analysis 3.7), length (Analysis 3.8), head circumference (Analysis 3.9) or Bayley mental score (Analysis 3.10).

### Isocaloric protein supplementation

Two trials, involving 184 women, were included. Owing to the significant heterogeneity in the results for birthweight and gestational weight gain, the data were pooled using a random-effects model. There was no significant effect on birthweight or gestational weight gain of isocaloric protein supplementation. For mean birthweight the MD was +108.25 g (95% CI -220.89 to 437.40, $Tau^2$ = 47211, $I^2$ = 84%; two trials, 184 infants - Analysis 4.1), while for gestational weight gain, the MD was +110.45 g/week (95% CI 82.87 to 303.76, $Tau^2$ = 16542, $I^2$ = 85%; two trials, 184 women - Analysis 4.2).

### Subgroup analysis in balanced energy/protein supplementation

Since observational studies (IOM 1990; Kramer 1987) suggested 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), (Huybregts 2009) and (Viegas 1982b), within-trial stratification was possible, based on the data contained in the published reports. Only the mean birthweight in balanced energy/protein supplementation

were analysed for the subgroups of undernourished and nourished women. However, there was no evidence of a subgroup differences between the malnourished and adequately nourished groups (test for subgroup differences: $Chi^2 = 2.35$. df = 1(P = 0.12), $I^2 = 57.5\%$).

## ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

**Balanced protein and energy supplementation compared to control or no intervention in pregnancy for perinatal and maternal outcomes**

**Patient or population:** Pregnant women
**Settings:**
**Intervention:** Balanced protein/energy supplementation in pregnancy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Balanced protein/ energy supplementation in pregnancy | | | | |
| Stillbirth | Study population | | RR 0.62 (0.4 to 0.98) | 3408 (5 studies) | ⊕⊕⊕○ **moderate**[1] | |
| | 28 per 1000 | 17 per 1000 (11 to 27) | | | | |
| | Moderate | | | | | |
| | 25 per 1000 | 15 per 1000 (10 to 25) | | | | |
| Neonatal death | Study population | | RR 0.68 (0.43 to 1.07) | 3381 (5 studies) | ⊕⊕○○ **low**[1,2] | |
| | 26 per 1000 | 18 per 1000 (11 to 28) | | | | |

| | | | | | |
|---|---|---|---|---|---|
| | **Moderate** | | | | |
| | **17 per 1000** | **12 per 1000** (7 to 18) | | | |
| **Birthweight (g)** | | The mean birthweight (g) in the intervention groups was **40.96 higher** (4.66 to 77.26 higher) | | 5385 (11 studies) | ⊕⊕⊕○ **moderate**[1] |
| **Small-for-gestational age** | **Study population** | | **RR 0.79** (0.69 to 0.9) | 4408 (7 studies) | ⊕⊕⊕○ **moderate**[1] |
| | **173 per 1000** | **137 per 1000** (120 to 156) | | | |
| | **Moderate** | | | | |
| | **163 per 1000** | **129 per 1000** (112 to 147) | | | |
| **Preterm birth** | **Study population** | | **RR 0.96** (0.8 to 1.16) | 3384 (5 studies) | ⊕⊕⊕○ **moderate**[3] |
| | **112 per 1000** | **108 per 1000** (90 to 130) | | | |
| | **Moderate** | | | | |
| | **113 per 1000** | **108 per 1000** (90 to 131) | | | |
| **Pre-eclampsia** | **Study population** | | **RR 1.48** (0.82 to 2.66) | 463 (2 studies) | ⊕○○○ **very low**[1,2,4] |
| | **73 per 1000** | **108 per 1000** (60 to 195) | | | |
| | **Moderate** | | | | |

| | | |
|---|---|---|
| | **38 per 1000** | **56 per 1000** (31 to 101) |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Allocation concealment, blinding, incomplete outcome reporting is high risk of bias in some studies.
[2] Wide 95% CI.
[3] Random sequence, allocation concealment is unclear in some studies.
[4] Sample size is smaller than optimal information size.

**High protein supplementation in pregnancy and perinatal outcomes**

**Patient or population:** Pregnant women
**Settings:**
**Intervention:** High protein supplementation in pregnancy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | High protein supplementation in pregnancy | | | | |
| **Stillbirth** | **Study population** | | **RR 0.81** (0.31 to 2.15) | 529 (1 study) | ⊕⊕◯◯ **low**[1,2] | |
| | **33 per 1000** | **27 per 1000** (10 to 72) | | | | |
| | **Moderate** | | | | | |
| | **33 per 1000** | **27 per 1000** (10 to 71) | | | | |
| **Neonatal death** | **Study population** | | **RR 2.78** (0.75 to 10.36) | 529 (1 study) | ⊕⊕◯◯ **low**[1,2] | |
| | **11 per 1000** | **31 per 1000** (8 to 115) | | | | |
| | **Moderate** | | | | | |
| | **11 per 1000** | **31 per 1000** (8 to 114) | | | | |
| **Small-for-gestational age** | **Study population** | | **RR 1.58** (1.03 to 2.41) | 505 (1 study) | ⊕⊕⊕◯ **moderate**[2] | |

| | | | | | |
|---|---|---|---|---|---|
| | **117 per 1000** | **185 per 1000** (121 to 282) | | | |
| | **Moderate** | | | | |
| | **117 per 1000** | **185 per 1000** (121 to 282) | | | |
| **Birthweight (g)** | | The mean birthweight (g) in the intervention groups was **73 lower** (171.26 lower to 25.26 higher) | | 504 (1 study) | ⊕⊕◯◯ **low**[1,2] |
| **Preterm birth** | **Study population** | | **RR 1.14** (0.83 to 1.56) | 505 (1 study) | ⊕⊕◯◯ **low**[1,2] |
| | **219 per 1000** | **249 per 1000** (182 to 341) | | | |
| | **Moderate** | | | | |
| | **219 per 1000** | **250 per 1000** (182 to 342) | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Wide 95% CI.
[2] Sample size is smaller than optimal information size.

**Isocaloric balanced protein supplementation in pregnancy and outcomes**

**Patient or population:** Pregnant women
**Settings:**
**Intervention:** Isocaloric balanced protein supplementation in pregnancy

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of Participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Isocaloric balanced protein supplementation in pregnancy | | | | |
| **Birthweight (g)** | | The mean birthweight (g) in the intervention groups was **108.25 higher** (220.89 lower to 437.4 higher) | | 184 (2 studies) | ⊕○○○ **very low**[1,2,3] | |
| **Weekly gestational weight gain (g/week)** | | The mean weekly gestational weight gain (g/week) in the intervention groups was **110.45 higher** (82.87 lower to 303.76 higher) | | 184 (2 studies) | ⊕○○○ **very low**[1,3,4] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval;

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1] Two trials are unclear risk of random sequence generation, allocation concealment, blinding, and selective reporting.
[2] I-square is 84%, P value = 0.01.
[3] Sample size is smaller than optimal information size.
[4] I-square is 85% with P value 0.01.

# DISCUSSION

## Summary of main results

Nutritional advice was successful in reducing the risk of preterm birth, increasing head circumference at birth and increasing protein intake, however, there was no evidence of benefit or adverse effect for any other outcome reported.

Balanced energy/protein supplementation was associated with significantly reduced risk of stillbirth, increased mean birthweight, and a significant reduction in the risk of small-for-gestational-age birth. No significant effect was detected for preterm birth, or neonatal death.

High-protein supplementation was associated with a significantly increased risk of infants born small-for-gestational age, but this is based on only one trial including 1051 women. Isocaloric protein supplementation had no significant effect on birthweight or weekly gestational weight gain, based on two trials including only 184 women.

## Overall completeness and applicability of evidence

Nutritional advice appears effective in increasing pregnant women's protein intake, reducing preterm birth and significant increases in birth head circumference. No data have been reported on other important maternal pregnancy outcomes, such as duration of labour, caesarean section, or postpartum weight retention. The modest increase in birthweight associated with balanced energy/protein supplementation may well be explained by the rather small net increases in energy intake achieved in most of the trials. Noncompliance and dietary substitution are likely explanations for these small net increases, and the much higher energy supplement provided in the Gambia trial (Ceesay 1997) appeared to have a much larger effect on mean birthweight. Of the seven sizeable trials with the highest methodological quality (Blackwell 1973; Ceesay 1997; Elwood 1981; Huybregts 2009; Kardjati 1988; Mora 1978; Rush 1980), only the East Java trial (Kardjati 1988) failed to show any benefit for mean birthweight (Analysis 2.3), despite convincing evidence that the trial participants were under-nourished prior to the intervention. Owing to the large sample size, chance is an unlikely explanation for the absence of benefit in the East Java trial( Kardjati 1988), and an undetected substitution of the normal home diet by the supplement seems more likely. Due to the significant effect on mean birthweight (Analysis 2.3), the reduction in the risk of infant born in small-for-gestational age (Analysis 2.6) was substantial. Nonetheless, that reduction did not appear to be associated with long-term benefits for child growth or development, but long-term follow-up was only reported in two trials (Ceesay 1997; Rush 1980). Of greatest importance is the evidence indicating reduced risk of stillbirth (Analysis 2.1). However, this evidence is based on five trials and the evidence is classified as low quality, and the biological mechanism for such risk reduction remains unclear, given the modest effects observed on the indices of fetal growth.

Most of the supplements/dietary manipulations also involved changes to the micronutrient (vitamins and minerals) content of the diet in the both intervention and control. As micronutrient supplementation may also alter some pregnancy outcomes independent of protein and energy, it is difficult to separate the contribution to the effects, particularly in the "balanced protein and energy" studies.

The available evidence from one trial provides no justification for prescribing high-protein nutritional supplements to pregnant women. Not only do such supplements appear to lack beneficial effects, but the evidence suggests that they may even be harmful. Furthermore, the data derived from these trials suggest that isocaloric protein supplementation alone (i.e. without energy supplementation) is unlikely to be of benefit to pregnant women or their infants. The included two trials had high heterogeneity, probably because amounts of energy supplementation were different (273 kcal in Viegas 1982a; 425 kcal in Viegas 1982b). The finding of the excluded trial of Mardones 1988, which reported increases in the risk of infant born small-for-gestational age, remains uncertain, given the methodological limitations of the trial. Moreover, the normal-protein "control" supplement in Mardones 1988 contained much higher quantities of iron and other micronutrients than the high protein supplement.

The results of this review should be interpreted with caution considering that the majority of trials were published in 1970/1980s. The incidence of inadequate nutrition and overweight and obesity is likely to be different today and most trials included a mixed population of those considered to have poor nutritional status and potentially those with adequate nutrition or over-nutrition. Indeed seven trials were from high-income countries where recent reports suggest two-thirds of the general population and half of pregnant women are overweight or obese (Haslehurst 2006; Wang 2011).

## Quality of the evidence

We included 15 trials involving 7410 women. The quality of the evidence in this review is assessed using the GRADE approach (Guyatt 2008) and the results are presented in Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; and Summary of findings 4. The GRADE uses four levels of quality (very low, low, moderate and high) over several domains covering limitations in the design and implementation of the studies, indirectness of evidence, unexplained heterogeneity or inconsistency in the results, imprecision of the results and high probability of publication bias. In the nutritional advice during pregnancy studies (Summary of findings for the main comparison), the evidence was judged to be of moderate quality