# Energy and protein intake in pregnancy (Review)

**Kramer MS, Kakuma R**


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## ABSTRACT

**Background**
Gestational weight gain is positively associated with fetal growth, and observational studies of food supplementation in pregnancy have reported increases in gestational weight gain and fetal growth.

**Objectives**
To assess the effects of advice to increase or reduce energy or protein intake, or of actual energy or protein supplementation or restriction, during pregnancy on energy and protein intakes, gestational weight gain, and the outcome of pregnancy.

**Search strategy**
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (November 2006) and contacted researchers in the field.

**Selection criteria**
Acceptably controlled trials of dietary advice to increase or reduce energy or protein intake, or of actual energy or protein supplementation or restriction, during pregnancy.

**Data collection and analysis**
We extracted data from published reports, supplemented by additional information from the trialists we contacted.

**Main results**
In five trials (1134 women), nutritional advice to increase energy and protein intakes was successful in achieving those goals, but no consistent benefit was observed on pregnancy outcomes.

In 13 trials (4665 women), balanced energy/protein supplementation was associated with modest increases in maternal weight gain and in mean birthweight, and a substantial reduction in risk of small-for-gestational-age (SGA) birth. These effects did not appear greater in undernourished women. No significant effects were detected on preterm birth, but significantly reduced risks were observed for stillbirth and neonatal death.

In two trials (529 women), high-protein supplementation was associated with a small, nonsignificant increase in maternal weight gain but a nonsignificant reduction in mean birthweight, a significantly increased risk of SGA birth, and a nonsignificantly increased risk of neonatal death. In three trials, involving 966 women, isocaloric protein supplementation was also associated with an increased risk of SGA birth.

In three trials (384 women), energy/protein restriction of pregnant women who were overweight, or exhibited high weight gain, significantly reduced weekly maternal weight gain and mean birthweight but had no effect on pregnancy-induced hypertension or pre-eclampsia.

**Authors' conclusions**
Dietary advice appears effective in increasing pregnant women's energy and protein intakes but is unlikely to confer major benefits on infant or maternal health.

Balanced energy/protein supplementation improves fetal growth and may reduce the risk of fetal and neonatal death. High-protein or balanced-protein supplementation alone is not beneficial and may be harmful to the fetus.

Protein/energy restriction of pregnant women who are overweight, or exhibit high weight gain, is unlikely to be beneficial and may be harmful to the fetus.

## PLAIN LANGUAGE SUMMARY

Energy and protein intake in pregnancy

A baby developing inside the womb receives all its nutrition from its mother. Thus, advising women on diet and providing food supplements in pregnancy may help babies to grow and thrive, particularly babies of undernourished mothers. The review of trials examined several aspects of this and found:
(1) nutritional advice: 5 trials involving 1134 women showed an increase in the mother's energy intake but no clear benefit for the developing baby;
(2) giving energy and protein balanced supplements, including to undernourished women: 13 trials involving 4665 women showed fewer small babies and fewer stillbirths, but the impact on long-term health of the baby is uncertain;
(3) high-protein supplementation: 2 trials involving 1076 women: showed no benefit for babies or women;
(4) isocaloric protein supplements (i.e. without energy supplementation): 3 trials involving 966 women showed no benefit and potential harm;
(5) energy/protein restriction in women with overweight or high-weight gain: 3 trials involving 384 women found no benefit and potential harm to the developing baby.
The overall findings suggest nutritional advice to women and balanced energy/protein supplements may be beneficial but that high-protein supplements for pregnant women and energy/protein restriction for overweight pregnant women may both be harmful.

## BACKGROUND

Observational studies (Kramer 1987; IOM 1990; Rush 2001) have reported 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 prepregnancy weight-for-height. The Dutch Famine Study (Stein 1975) found a clear reduction in fetal growth, but no effect on gestational duration when pregnant women were forced by the Germans in 1944 and 1945 to reduce their energy intake during the third trimester. Non-randomized trials of 'balanced' energy/protein supplementation (i.e., supplements in which protein provides less than 25% of the total energy content) have reported beneficial effects on fetal growth (Lechtig 1975; Prentice 1983) although the evidence from properly randomized trials suggests more modest benefits (Rush 1989; Rush 2001). Trials of interventions to increase fetal growth have taken on greater interest in light of recent evidence that higher birthweight for gestational age is associated with reduced risks for Type II diabetes, hypertension, and coronary heart disease in late adulthood (Barker 1998).

Data from animal studies and human trials suggest that high-protein dietary supplementation (i.e., supplementation in which the protein provides at least 25% of its total energy content) may adversely affect pregnancy outcome (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 replaces an equivalent amount of energy in the diet. The observational findings reported from a non-randomized trial in Guatemala (Lechtig 1975) also suggest that protein supplementation is unlikely to benefit pregnant women or their infants.

Rapid weight gain during pregnancy has long been recognized as a clinical sign of fluid retention and impending pre-eclampsia, and large weight gains are associated with postpartum maternal weight retention. Before 1970, clinicians frequently counseled pregnant women to restrict their food intake in an attempt to prevent pre-eclampsia, despite the absence of evidence that such advice was beneficial. Moreover, evidence from observational studies (including the Dutch Famine Study (Stein 1975)) strongly suggests that such restriction (among non-obese women, at least) is associated with impairment in fetal growth. No evidence points to specific effects of protein (as opposed to energy) restriction, although prescription of a well-balanced diet that restricts energy intake will also lead to a reduction in protein intake.

## OBJECTIVES

The objectives of this review are to assess the effects of dietary advice, supplementation, or restriction on gestational weight gain, pre-eclampsia, and/or pregnancy outcomes. More specifically, the purpose of this review was to determine the effects of:
(1) advising pregnant women to increase their energy and protein intakes on those intakes, on gestational weight gain, and on the

outcome of pregnancy, including fetal growth, gestational duration, and maternal and fetal/infant morbidity and mortality;
(2) balanced energy/protein supplements during pregnancy on gestational weight gain and the outcome of pregnancy;
(3) high-protein nutritional supplements during pregnancy on gestational weight gain and on the outcome of pregnancy;
(4) isocaloric protein supplements (i.e., where the protein replaces an equal quantity of nonprotein energy) during pregnancy on gestational weight gain and on the outcome of pregnancy; and
(5) prescribing a low-energy diet to pregnant women who are either overweight, or who exhibited high weight gain earlier in gestation, on subsequent weight gain, pre-eclampsia, and the outcome of pregnancy.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

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

For assessing dietary supplementation, all randomized and quasi-randomized controlled trials of energy/protein supplementation.

For assessing dietary restriction, all randomized and quasi-randomized controlled trials of energy/protein restriction prescribed to pregnant women who are overweight and/or exhibited high weight gain during pregnancy.

### Types of participants

Pregnant women.

For the assessment of dietary restriction, pregnant women with either high pregnancy weight or high gestational weight gain.

### Types of intervention

Specific advice to increase dietary energy and protein intakes, energy and/or protein supplementation, or prescription of low-energy diet. For energy and protein supplementation, no minimum protein content was required; trials of nonprotein energy are therefore included. Types of supplements included those that were 'balanced' energy/protein supplements (the protein provided less than 25% of the total energy content), high-protein supplements (the protein provided 25% of the total energy content), and isocaloric protein supplements (balanced supplements in which the protein replaced an equal quantity of nonprotein energy).

### Types of outcome measures

Dietary intake; gestational weight gain; pregnancy outcome for the fetus/infant (stillbirth, neonatal death, fetal growth, gestational duration), child (growth and development), and mother (complications of pregnancy, labor, and delivery, postpartum weight retention).

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (November 2006).

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) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We contacted authors for additional data.

We did not apply any language restrictions.

## METHODS OF THE REVIEW

### Selection of studies

We have assessed for inclusion all potential studies we identified as a result of the search strategy, without consideration of the results. We resolved any disagreement through discussion.

### Data extraction and management

Both review authors extracted the data using the agreed form. We used the Review Manager software (RevMan 2003) to double-enter all data.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

**Assessment of methodological quality of included studies**
We assessed the validity of each study using the criteria outlined in the Cochrane Handbook (Higgins 2005). Methods used for generation of the randomization sequence have been described for each trial.

***(1) Randomization and allocation concealment***
We assigned a quality score for each trial, using the following criteria:
(A) adequate concealment of allocation: such as telephone randomization, consecutively numbered sealed opaque envelopes;
(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;
(C) inadequate concealment of allocation: such as open list of random number tables, use of case record numbers, dates of birth or days of the week.

***(2) Attrition bias (loss of participants, e.g. withdrawals, dropouts, protocol deviations)***
We assessed completeness to follow up using the following criteria:
(A) less than 5% loss of participants;
(B) 5% to 9.9% of loss of participants;
(C) 10% to 19.9% loss of participants;
(D) more than 20% loss of participants.

***(3) Outcomes measurement bias (blinding of participants, researchers and outcome assessment)***
We assessed blinding using the following criteria:
(1) blinding of participants (yes/no/unclear);
(2) blinding of caregiver (yes/no/unclear);
(3) blinding of outcome assessment (yes/no/unclear).

**Measures of treatment effect**
We carried out statistical analysis using the Review Manager software (RevMan 2003). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity if trials were sufficiently similar. If heterogeneity was found, we used random-effects meta-analysis.

**Dichotomous data**
For dichotomous data, we have presented results as summary relative risk with 95% confidence intervals.

**Continuous data**
For continuous data, we have used the weighted mean difference when outcomes were measured in the same way between trials.

**Unit of analysis issues**

***Cluster-randomized trials***
We included cluster-randomized trials in the analyses along with individually randomized trials. Their sample sizes were adjusted using the methods described in Gates 2005 using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. Two of the trials (Ceesay 1997; Kafatos 1989) gave no published or unpublished data on the outcome-specific ICC; we have assumed a value of .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 .01).

**Dealing with missing data**
We have analysed data on all participants with available data in the group to which they were allocated, regardless of whether or not they received the allocated intervention. If in the original reports participants were not analysed in the group to which they were randomized, and there was sufficient information in the trial report, we would have attempted to restore them to the correct group.

**Assessment of heterogeneity**
We have applied tests of heterogeneity between trials, if appropriate, using the $I^2$ statistic. If we identified high levels of heterogeneity among the trials (exceeding 50%), we have explored it by performing sensitivity analysis. A random-effects meta-analysis was used as an overall summary when considered appropriate.

Because observational studies (Kramer 1987; IOM 1990) suggest a stronger association between gestational weight gain and fetal growth in women who are under-nourished before pregnancy, we stratified the analysis of effects on mean birthweight into those trials in which the majority of women had low pre-pregnancy (or early pregnancy) weight (Atton 1990; Campbell Brown 1983; Ceesay 1997; Girija 1984; Kardjati 1988; Mora 1978; Rush 1980), and those in which the participants seemed adequately nourished (Elwood 1981; Ross 1985; Viegas 1982a). For the Taiwan trial (Blackwell 1973) and Viegas 1982b, within-trial stratification was possible, based on data contained in the published reports.

## DESCRIPTION OF STUDIES

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

## METHODOLOGICAL QUALITY

The overall methodological quality of the trials on dietary advice is not high. Only Kafatos 1989 and Sweeney 1985 documented random, unbiased allocation. Briley 2002; Hankin 1962; and Hunt 1976 all excluded a number of participants after allocation, and Kafatos 1989 based its analysis on individual women, even though randomization was by clinic. None of the trials mentioned blinding of the observers who measured dietary intake, and women randomized to receive advice in Kafatos 1989 had considerably higher energy intakes prior to randomization than did the control women.

The 13 included trials on the impact of balanced energy/protein supplementation are of variable quality; the major methodological defects being the failure to provide details of the treatment allocation procedure and the exclusion, after allocation, of women who were unable or unwilling to take their allocated supplements. The degree of compliance and substitution of the normal diet may also have been quite variable across the trials; these characteristics can be assessed only imprecisely with available methods (dietary recall). The best of the reasonably-sized trials are those from Taiwan (Blackwell 1973), Harlem (Rush 1980), Wales (Elwood 1981), Bogota (Mora 1978), East Java (Kardjati 1988), and the Gambia (Ceesay 1997).

For the assessment of high-protein nutritional supplements, the Harlem trial (Rush 1980) is of high quality; its only drawback being the exclusion of a small number of women unable or unwilling to take their supplements. The Iyengar 1967 trial does not describe the treatment allocation procedure used, nor the total number of women allocated and the number who failed to comply or were otherwise not analyzed.

Neither of the two small trials on the effect of isocaloric protein supplements by Viegas (Viegas 1982a; Viegas 1982b) adequately described the allocation procedure used, but both were otherwise of high quality. Mardones 1988 used alternate allocation and suffered from large, but apparently unbiased, losses to follow up.

None of the trials of energy/protein restriction specified the method of allocation. In the Campbell 1975 trial, data on birthweight and anthropometry in later childhood (centiles only) were presented only for women not developing pre-eclampsia and have therefore been excluded from this review.

## RESULTS

**Nutritional advice to increase energy and protein intakes**

Five trials of nutritional advice, involving 1134 women, were included. Within the methodological limitations discussed above, advice to increase energy and protein intakes seems to be successful in achieving those goals (weighted mean difference (WMD) 105.61, 95% confidence interval (CI) -18.94 to 230.15, kcal/day for energy intake and WMD 17.99, 95% CI -1.48 to +37.45, g/day for protein), but the increases are lower than those reported in trials of actual protein/energy supplementation. Data concerning effects on maternal weight gain, fetal growth, gestational duration, preterm birth, and fetal and neonatal mortality are available only from Kafatos 1989 (which have been adjusted for a presumed within-clinic intra-class correlation of .01) and Briley 2002. Moreover, the 'significant' reduction in preterm birth associated with advice (relative risk (RR) 0.46, 95% confidence interval (CI) 0.21 to 0.98) is not consistent with the total absence of effect on mean gestational age (WMD -0.10, 95% CI -0.48 to 0.28, week). Hankin 1962 found no reduction in the incidence of pre-eclampsia (RR 0.89, 95% CI 0.42 to 1.88). No data have been reported on other maternal pregnancy outcomes, such as duration of labour, cesarean section, or postpartum weight retention.

**Balanced energy/protein supplementation**

Thirteen trials, involving 4665 women, were included. Because of significant heterogeneity in the results for gestational weight gain, the data have been pooled using a random-effects model, yielding a small but significant increase with supplementation (random effects WMD 20.74, 95% CI 1.46 to 40.02, g/week).

Supplementation was also associated with an increase in mean birthweight (random effects WMD 37.62, 95% CI -0.21 to 75.45, g). No statistically significant differences were found in birth length and birth head circumference. However, the incidence of small-for-gestational-age (SGA) birth was reduced substantially (RR 0.68, 95% CI 0.56 to 0.84). The stratified analysis showed a nonsignificantly larger effect of supplementation on mean birthweight in under-nourished women. Considerably larger effects on fetal growth, however, were reported from a trial in under-nourished women from the Gambia (Ceesay 1997) that provided much higher energy supplements. Of the six sizeable trials of highest methodological quality (Blackwell 1973; Ceesay 1997; Elwood 1981; Kardjati 1988; Mora 1978; Rush 1980), only the East Java trial (Kardjati 1988) failed to show any benefit on fetal growth, despite convincing evidence that trial participants were undernourished prior to the intervention. Because of the large sample size, chance is an unlikely explanation for the absence of benefit in the East Java trial; an undetected substitution of the normal home diet by the supplement seems more likely.

Although postnatal follow up was limited to only a few trials, the enhancement of fetal growth observed in those trials was not reflected in larger size or improved neurocognitive development at one year. The Taiwan trial (Blackwell 1973) detected no effect on Stanford-Binet IQ score at five years.

The available data exclude, with high probability, an important effect of supplementation on mean gestational age but paradoxically suggest a (nonsignificantly) reduced risk of preterm birth. This inconsistency could reflect problems in gestational age measurement (possible misclassification of SGA infants as preterm) or the fact that the two trials with the largest reduction in preterm birth (Blackwell 1973; Rush 1980) did not report results for mean gestational age.

Reductions in stillbirth (RR 0.55, 95% CI 0.31 to 0.97) and neonatal death (RR 0.62, 95% 0.37 to 1.05) are based on only four trials but appear important.

Maternal outcomes other than weight gain have been reported very infrequently. The rather meagre data on pre-eclampsia do not suggest a reduced risk with supplementation (RR 1.20, 95% CI 0.77 to 1.89). Only one trial each reported results on other outcomes. The Bogota trial (Mora 1978) detected no significant reduction in duration of labour with supplementation. The East Java trial (Kardjati 1988) found no increase in maternal weight

four weeks postpartum associated with supplementation nor a significant increase in breast milk output at two to three months. No data have been reported on cesarean section.

**High-protein supplementation**

Two trials (Iyengar 1967; Rush 1980), involving 1076 women, were included. The meta-analysis on the effect of high-protein nutritional supplements principally reflects the results of the Harlem trial (Rush 1980), because of its larger size. High-protein supplementation was associated with no difference in weekly maternal weight gain (WMD 2.98, 95% CI -33.03 to 38.99, g/week). The two available trials (Iyengar 1967; Rush 1980) provide no evidence of benefit on fetal growth; indeed, the weighted mean difference in birthweight is -58.37 (95% CI -146.23 to 29.50) g. At one-year follow up in the Harlem trial (Rush 1980), high-protein supplementation was not associated with a detectable difference in weight, length, head circumference, or Bayley mental score. The Harlem trial (Rush 1980) reported a nonsignificantly increased risk of neonatal death with high-protein supplementation (RR 2.78, 95% CI 0.75 to 10.36), but also reported a small, nonsignificant reduction in stillbirth (RR 0.81, 95% CI 0.31 to 2.15).

**Isocaloric protein supplementation**

Three trials, involving 966 women, were included. The meta-analysis on the effect of isocaloric protein supplements principally reflects the data reported from the large Mardones 1988 trial. Because of significant heterogeneity in the results for gestational weight gain and birthweight, the data have been pooled using a random-effects model. For gestational weight gain, the WMD is 51.68 (95% CI -75.06 to 178.42) g/week, while for mean birthweight, the WMD is 33.45 (95% CI -157.88 to 224.77) g. The Mardones 1988 trial, however, found an increased risk of small-for-gestational-age (SGA) birth (RR 1.35, 95% CI 1.12 to 1.61) with isocaloric protein supplementation; no effect was observed on mean gestational age or preterm birth. The data are insufficient to exclude potentially important effects on fetal or neonatal mortality, and maternal health outcomes have not been reported.

**Energy/protein restriction in women with overweight or high weight gain**

Three trials, involving 384 women, were included. Both Campbell trials (Campbell 1975; Campbell 1983) reported that energy/protein restriction was associated with a significant reduction in weekly maternal weight gain, although the magnitude of the reduction was much larger in the 1975 trial (random effects WMD -254.81 (95% CI -436.56 to -73.06) g/week). Energy/protein restriction had no effect on either (proteinuric) pre-eclampsia or pregnancy-induced hypertension (with or without proteinuria), although the small number of trials and participants provides inadequate statistical power to exclude a small effect. The two trials reporting on birthweight (Badrawi 1993; Campbell 1983) yielded highly (and statistically significantly) heterogeneous results, with Campbell 1983 reporting virtually no effect of the intervention (WMD 6.00, 95% CI -121.55 to +133.55, g) but Badrawi 1993 finding a large significant adverse effect (WMD -450.00 (95% CI -624.72 to -275.28) g). These large differences in results could reflect either differences in study samples (Scotland versus Egypt) or differences in the degree of energy/protein restriction achieved. Only Campbell 1983 reported results bearing on gestational duration; the results appear to exclude an important adverse effect of dietary restriction (WMD in mean gestational age = +0.25 (-0.17 to +0.67) week). Other outcomes, including fetal/infant mortality and other measures of maternal morbidity (e.g., cesarean section) or postpartum weight retention, have not been reported.

## DISCUSSION

Nutritional advice appears effective in increasing pregnant women's energy and protein intakes, but the implications for fetal, infant, or maternal health cannot be judged from the available trials. Given the rather modest health benefits demonstrated with actual protein/energy supplementation, however, the provision of such advice is unlikely to be of major importance.

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; the much higher energy supplement provided in the Gambian trial (Ceesay 1997) appeared to have a much larger effect on mean birthweight. Despite the modest overall effect on mean birthweight, the reduction in risk of SGA birth has been substantial. Nonetheless, that reduction does not appear to be associated with long-term benefits for child growth or development. The observed nonsignificant reduction in preterm birth with supplementation would probably be of greater importance, if confirmed in subsequent trials, but is not consistent with the absence of any effect on mean gestational age (unless the reduction in preterm birth is accompanied by a counterbalancing reduction in post-term birth, which seems unlikely). Perhaps of greatest importance is the evidence indicating reduced risk of fetal and neonatal death. This evidence is based on only four trials, however, and the biological mechanism for such risk reduction is unclear, given the modest effects observed on indices of fetal growth and the uncertain effect on gestational duration.

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. Furthermore, the data derived from these trials suggest that isocaloric protein supplementation alone (that is, without energy supplementation) is unlikely to be of benefit to pregnant women or their infants. This conclusion appears to apply even to undernourished women (all of the women in the Mardones 1988 trial and at least some

of the women in the second Viegas trial); it also confirms the observational findings reported from a non-randomized trial in Guatemala. Whether isocaloric protein supplementation actually increases the risk of fetal growth restriction, as suggested by the findings of Mardones 1988 for SGA birth, is uncertain, given the methodological limitations of that trial. Moreover, the normal-protein "control" supplement in Mardones 1988 contained much higher quantities of iron and other micronutrients than the higher-protein supplement. A slight reduction in risk of SGA birth has been observed in a Cochrane review of multiple-micronutrient supplementation compared with supplementation with two or fewer micronutrients or a placebo, but not when compared with supplementation with iron and folic acid (Haider 2006).

The limited evidence available suggests that protein/energy restriction of pregnant women who are overweight, or exhibit high weight gain, is unlikely to be beneficial and may be harmful to the developing fetus.

## AUTHORS' CONCLUSIONS

### Implications for practice

Nutritional advice appears effective in increasing pregnant women's energy and protein intakes, but the implications for fetal, infant, or maternal health cannot be judged from the available trials. Given the rather modest health benefits demonstrated with actual protein/energy supplementation, however, the provision of such advice is unlikely to be of major importance.

Balanced protein/energy supplementation, as provided in most trials, results in modest increases in maternal weight gain and fetal growth. These increases do not appear significantly larger in undernourished women, nor do they seem to confer long-term benefits to the child in terms of growth or neurocognitive development. The increases do appear larger, however, when the energy content of the supplement is very high. Supplementation also appears to reduce the risks of stillbirth and of neonatal death, although the biological mechanisms underlying this reduction remain unclear. The available evidence is inadequate to evaluate potential effects on preterm birth or maternal health.

There is no justification for prescribing high-protein nutritional supplements to pregnant women given the available data. Not only do such supplements appear to lack beneficial effects, the evidence suggests that they may even be harmful. Furthermore, the data derived from the included trials suggest that isocaloric protein supplementation alone (i.e., without energy supplementation) is unlikely to be of benefit to pregnant women or their infants. Moreover, the possibility that isocaloric protein supplementation actually increases the risk of fetal growth restriction cannot be dismissed.

The limited evidence available from the three included trials suggests that energy/protein restriction of pregnant women who are overweight, or exhibit high weight gain, may impair fetal growth and is of no benefit in reducing the risk of pre-eclampsia or pregnancy-induced hypertension. In the absence of data suggesting a reduced risk of cesarean section or maternal postpartum weight retention, protein/energy restriction during pregnancy cannot be recommended.

### Implications for research

Given the modest benefits documented with balanced protein/energy supplementation, it is difficult to make any research recommendations concerning future research on nutritional advice to increase the intake of these macronutrients.

Future energy/protein supplementation trials should focus their attention on outcomes other than fetal growth, and especially on confirming the evidence of reduced risk of stillbirth and neonatal death. Such trials will require large sample sizes. Any future trials should also assess the effects on women, including duration of labour, cesarean section, and postpartum weight retention.

The lack of evidence of benefit, coupled with the possibility of harm, suggests that future trials of high-protein supplementation, isocaloric protein supplementation, or protein/energy restriction during pregnancy are not indicated.

## NOTES

History of review development

August 2003
This updated review combines and replaces five previous Cochrane reviews entitled "Balanced protein/energy supplementation in pregnancy' , 'Energy/protein restriction for high weight-for-height or weight gain during pregnancy' , 'High protein supplementation in pregnancy' , 'Isocaloric balanced protein supplementation in pregnancy' and 'Nutritional advice in pregnancy'.

This combination was suggested by colleagues in the field, the PCG editors, and by the Cochrane Pregnancy and Childbirth Group's Consumer Panel.

## POTENTIAL CONFLICT OF INTEREST

None known.

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### External sources of support

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### Internal sources of support

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** Indicates the major publication for the study*

# TABLES

## Characteristics of included studies

| **Study** | **Atton 1990** |
|---|---|
| Methods | Alternate allocation. |
| Participants | 148 non-obese Asian women with triceps skinfold increase <= 2 mm from 18 to 28 weeks. |
| Interventions | Experimental: flavoured milk supplement containing 407 kcal energy and 14.6 g protein.<br>Control: normal (unsupplemented) diet. |
| Outcomes | Mean gestational age, birthweight, length, and head circumference. |
| Notes | 1) Authors claim alternate allocation, but numbers of women are equal in both treatment groups after excluding non-compliers.<br>2) 25 non-compliers excluded from analysis.<br>3) No data provided on total intake (and therefore on substitution or redistribution in family).<br>4) Slight discrepancy in mean birthweight data in Tables 4 versus 5. |
| Allocation concealment | C – Inadequate |

| **Study** | **Badrawi 1993** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 100 obese multiparous Egyptian women age 25-35 years. |
| Interventions | Experimental: balanced low-energy (1500-2000 kcal/day) diet. Control: normal diet according to WHO energy recommendations (2300-3000 kcal/day). |
| Outcomes | Gestational weight gain, birthweight, and PIH. |
| Notes | 1) Criteria for obesity not reported.<br>2) Follow up and method of analysis not reported.<br>3) Definition of PIH unclear.<br>4) Data on gestational weight gain contradictory in letter versus publication. |
| Allocation concealment | C – Inadequate |

| **Study** | **Blackwell 1973** |
|---|---|
| Methods | Interventions 'assigned randomly and blindly', but method not specified. |
| Participants | Well-nourished rural Taiwanese women with 'marginal' diets (estimated daily protein intake <= 40 g). |
| 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.<br>Control: supplement containing vitamins and minerals only, but given at same times and for same duration. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Outcomes | Gestational weight gain, preterm birth, birthweight, SGA, length, head circumference, and IQ at age 5. |
| Notes | 1) Data presented on dietary substitution, but based on meal survey only.<br>2) High alleged net energy supplement not associated with significantly higher gestational weight gain.<br>3) Discrepancies in first-infant LBW rates in 1981 versus 1973 reports.<br>4) Significant correlation between birthweight and energy (and supplement) intake in controls only.<br>5) Supplementation continued until 15 months postpartum; data on maternal postpartum weight therefore omitted from review. |
| Allocation concealment | B – Unclear |

| **Study** | **Briley 2002** |
|---|---|
| Methods | Randomization method not reported. |
| Participants | 27 low-income African-American women. |
| Interventions | Experimental: minimum of 6 individualized in-home nutrition assessment and counseling visits.<br>Control: 2 home visits without counseling. |
| Outcomes | Energy intake, gestational weight gain, birthweight, and preterm birth. |
| Notes | 1) 7 of 27 randomized women dropped out and not included in analysis.<br>2) Neither participants nor observers apparently blind to allocation. |
| Allocation concealment | B – Unclear |

| **Study** | **Campbell 1975** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 153 primiparous Scottish women with high gestational weight gain (> 1.25 lb or 570 g per week) between 20-30 weeks. |
| Interventions | Intervention: low-energy (1200 kcal/day), low-carbohydrate diet beginning at 30 weeks. Control: no intervention. |
| Outcomes | Gestational weight gain, PIH, and pre-eclampsia. |
| Notes | 1) Allocation method not reported.<br>2) Birthweight and anthropometry in later childhood reported only as percentiles and only in women without PIH or pre-eclampsia.<br>3) No report of compliance with diet. |
| Allocation concealment | C – Inadequate |

| **Study** | **Campbell 1983** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 182 obese (> 75th centile weight-for-height) primiparous Scottish women with normal IVGTT at 28 weeks. |
| Interventions | Intervention: low-energy (1250 kcal/day) diet. Control: no intervention. |
| Outcomes | Gestational weight gain, birthweight, birth length, gestational age, preterm birth, pre-eclampsia. |
| Notes | Gestational age calculable, but unclear whether completed weeks. |
| Allocation concealment | C – Inadequate |

| **Study** | **Campbell Brown 1983** |
|---|---|
| Methods | Strict alternate allocation. |
| Participants | 180 (90 matched pairs) Aberdeen primiparous women at high risk of low birthweight delivery because of low maternal height, weight or weight-for-height at 20 weeks, or weight gain between 20 and 30 weeks. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Interventions | Experimental: supplement of ½ pint flavoured milk drink or 1 pint fresh milk, or 75 g cheddar cheese; supplement contained 300 kcal energy and 15-20 g protein starting approximately 29 weeks of gestation.<br>Control: normal (unsupplemented) diet. |
| Outcomes | Gestational weight gain, preterm birth, birthweight, length, and head circumference. |
| Notes | 1) Good data on compliance and dietary substitution.<br>2) Gestational age data biased by replacement of women delivering < 37 weeks.<br>3) Reported overall preterm birth rate (9.7%) seems to be an error; should be 7.7%. |
| Allocation concealment | C – Inadequate |

| **Study** | **Ceesay 1997** |
|---|---|
| Methods | Cluster randomization 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). |
| 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.<br>Control villages: no supplement. |
| Outcomes | Gestational weight gain, gestational age, birthweight, birth length, head circumference, stillbirth, and neonatal death. |
| Notes | 1) Randomization 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 one pregnancy during study) baby.<br>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-randomized) 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'.<br>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 (63.81 experimental, 88.42 control) and r = 0.01 is the (assumed) intra-class correlation coefficient.<br>4) Number of intervention and control participants reversed in column headings of Table 5.<br>5) Data on immune function at age 6.5-9.5 years excluded from review, owing to 48% (but apparently unbiased) loss to follow up. |
| Allocation concealment | B – Unclear |

| **Study** | **Elwood 1981** |
|---|---|
| Methods | Randomization based on random numbers with sealed envelopes. |
| Participants | 1251 pregnant Welsh women in 2 small towns recruited at time of first reporting of pregnancy. |
| Interventions | Experimental: free tokens worth ½ pint milk each.<br>Control: no intervention. |
| Outcomes | Gestational age, preterm birth, birthweight, low birthweight, length, and head circumference. |
| Notes | 1) 24% of women lost to follow up, with evidence of higher losses in control group.<br>2) No adjustment for higher percentage of smokers in control group.<br>3) Trial also includes postnatal milk supplement (tokens) in children; all data on postnatal growth in children therefore omitted from review. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Allocation concealment | A – Adequate |

| **Study** | **Girija 1984** |
|---|---|
| Methods | Alternate allocation. |
| Participants | 20 poor Indian women in last trimester. |
| Interventions | Experimental: supplement containing 50 g sesame cake, 40 g jaggery, and 10 g oil (417 kcal energy and 30 g protein).<br>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.<br>2) No SDs reported on postnatal anthropometric outcomes, so data not included in review.<br>3) No data reported on compliance or dietary substitution.<br>4) Energy and protein intakes appear higher before supplementation, even in supplemented group.<br>5) Mean gestational age (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. |
| Allocation concealment | C – Inadequate |

| **Study** | **Hankin 1962** |
|---|---|
| Methods | Allocation by day of week. |
| Participants | 149 primigravid and secundigravid Australian women at first prenatal clinic visit (all < 20 weeks' gestation). |
| Interventions | Experimental: advice to improve quality (primarily to increase protein content) of diet, half with and half without additional dental advice. Control: no dietary advice. |
| Outcomes | Protein and energy intake, pre-eclampsia; no data on other pregnancy outcomes. |
| Notes | 1) 13 post-allocation exclusions for 'incomplete data'.<br>2) Increased protein intake documented by (? biased) 4-day dietary record. |
| Allocation concealment | C – Inadequate |

| **Study** | **Hunt 1976** |
|---|---|
| Methods | Method of randomization not reported. |
| Participants | 344 Spanish-speaking women with first prenatal clinic visit <= 21 weeks' gestation. |
| 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-randomization.<br>2) Possible 'contamination' via contact between women in two groups.<br>3) No blinding. |
| Allocation concealment | C – Inadequate |

| **Study** | **Iyengar 1967** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 25 low-SES Indian women 25-40 years engaged in manual labor with low energy and protein intakes at 36 weeks' gestation. |
| Interventions | Experimental: hospitalization + hospital diet + dietary supplement containing 100 g dry skimmed milk and providing 350 kcal energy and 35 g protein + iron and vitamins. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| | Control: same treatment without protein. |
| Outcomes | Gestational weight gain, birthweight, and maternal and cord blood total protein and albumin. |
| Notes | 1) Comparisons based on supplement vs complement, not supplement vs "control".<br>2) No information on total number of women allocated to treatments and losses to follow up.<br>3) No information on dietary compliance or substitution.<br>4) Slight discrepancies between Methods and Discussion in energy and protein intake figures. |
| Allocation concealment | C – Inadequate |

| **Study** | **Kafatos 1989** |
|---|---|
| Methods | Randomization of 20 clinics using computer-generated random numbers. |
| Participants | 568 pregnant women in rural area in Northern Greece < 27 weeks' gestation. |
| 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, gestational age, LBW, SGA, 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.<br>2) Dietary intake unblinded, and energy intake higher in experimental group prior to intervention.<br>3) Inconsistent results: lower preterm rate, yet no difference in mean GA; higher head and chest circumferences but no difference in birthweight.<br>4) Discrepancies in sample sizes for different outcomes, even birthweight versus LBW rate.<br>5) SEM of GA in intervention (experimental) group assumed to be 0.10, not the 0.01 shown in Table 3. |
| Allocation concealment | A – Adequate |

| **Study** | **Kardjati 1988** |
|---|---|
| Methods | "Blind" randomization based on household numbers, with use of random-numbers table. |
| Participants | 747 women in three villages in rural East Java (an area known to be 'nutritionally vulnerable') at 26-28 weeks' gestation. |
| 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').<br>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 analyzed according to intention-to-treat, they are included in this review because birthweight was similar in the 2 study groups and in non-compliers (both groups combined).<br>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.<br>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.<br>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 intention-to-treat). |
| Allocation concealment | A – Adequate |

| **Study** | **Mardones 1988** |
|---|---|
| Methods | Alternate treatment allocation, but no direct evidence of bias. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Participants | Low-income Chilean women < 20 weeks' gestation with low weight-for-height at first visit. |
| Interventions | Experimental: high-protein (approximately 22% of energy content) powdered milk supplement. Control: normal-protein (approximately 12% of energy content) powdered milk supplement. |
| Outcomes | Gestational weight gain, birthweight, length, head circumference, IUGR, LBW, gestational age, preterm birth, stillbirth, and neonatal death. |
| Notes | 1) Large losses seem unbiased.<br>2) Unbelievably similar baseline and outcome comparisons in 2 treatment groups (Tables 5 and 6).<br>3) Control supplement contained much higher quantities of iron and other micronutrients than experimental supplements. |
| Allocation concealment | C – Inadequate |

| **Study** | **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. |
| 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.<br>Control: normal (unsupplemented) diet. |
| Outcomes | Pre-eclampsia, gestational age, preterm birth, birthweight, low birthweight, stillbirth, perinatal mortality, neonatal mortality. |
| Notes | 1) Compliance assessed but data not presented.<br>2) Substitution assessed by single 24-hour recall 8 weeks after starting supplement.<br>3) Preterm birth rate not increased, but higher mortality reported among those born preterm: why?<br>4) Data on term LBW used in analysis of SGA. |
| Allocation concealment | C – Inadequate |

| **Study** | **Ross 1938** |
|---|---|
| Methods | Alternate allocation. |
| Participants | 56 young, poor primiparous women from rural North Carolina in maternity home with previous diets considered 'marginal' for quantity and quality of protein. |
| Interventions | Experimental: supplement containing 150 g skim milk powder, 20 yeast tablets, 15 drops percomorphum oil, 20 g bone meal, and 4 g ferrous sulfate (580 kcal energy and 60 gm protein).<br>Control: regular institution diet ('barely adequate'). |
| Outcomes | Pre-eclampsia, gestational weight gain. |
| Notes | 1) No data reported on compliance or dietary substitution.<br>2) Minor discrepancy in number of women (53, 54, or 56).<br>3) No apparent blinding.<br>4) Very high rate of pre-eclampsia overall (approximately 40% vs 15% historically at same institution).<br>5) Data on gestational weight gain presented only as means; SDs not reported, and thus data not included in review. |
| Allocation concealment | C – Inadequate |

| **Study** | **Ross 1985** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 127 Black South African women < 20 weeks' gestation. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| 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.<br>Control: placebo pills (zinc-supplemented group is excluded from review). |
| Outcomes | Gestational weight gain (after 20 weeks), gestational age, and birthweight. |
| Notes | 1) Study women averaged > 70 kg at 20 weeks.<br>2) Higher gestational weight gain in control group argues against causal association with birth weight.<br>3) No data presented on compliance or substitution.<br>4) Number of women originally randomized not reported ('90% continued ... to delivery').<br>5) Original sample size not given nor its justification. |
| Allocation concealment | C – Inadequate |

| **Study** | **Rush 1980** |
|---|---|
| Methods | Stratified randomization based on table of random numbers, with allocation in sealed envelope and blinding of all research staff. |
| Participants | 1051 low-income black women in Harlem (New York City) <= 30 weeks' gestation 'at risk' for low birthweight based on one or more of the following criteria: 1) pre-pregnancy weight < 110 lbs; 2) pre-pregnancy weight 110-139 lbs plus low gestational weight gain as of recruitment;<br>3) pre-pregnancy weight 110-139 lbs plus previous history of low birthweight; or<br>4) pre-pregnancy weight 110-139 lbs plus protein intake < 50 grams in the 24 hours preceding registration. |
| Interventions | Experimental (1): balanced energy/protein 16-oz beverage supplement containing 322 kcal energy, 6 g protein, and vitamins/minerals ('complement').<br>Experimental (2): high-protein 16-oz beverage supplement containing 470 kcal + 40 g protein per day + vitamins and minerals.<br>Control: supplement containing vitamins/minerals only. |
| Outcomes | Gestational weight gain, gestational age, preterm birth, SGA birth, birthweight, low birthweight, stillbirth, neonatal mortality, and weight, length, head circumference, and Bayley scores at 1 year. |
| Notes | Almost no data presented on the (approximately) 25% of participants who failed to comply, dropped out, or moved away. |
| Allocation concealment | A – Adequate |

| **Study** | **Sweeney 1985** |
|---|---|
| Methods | Stratified randomization 'using biased coin methodology'. |
| Participants | 47 healthy women < 20 weeks' gestation. |
| Interventions | Experimental: Higgins' method of protein/energy 'prescription' (i.e., advice only, no supplementation) Control: no advice. |
| Outcomes | Protein and energy intake, gestational weight gain, birthweight, and gestational age. |
| Notes | 1) Slight discrepancy in number of women allocated.<br>2) Mean and SD weight gain, birthweight, and GA not reported by allocation group.<br>3) Probable non-blinding of intake (protein and energy) histories. |
| Allocation concealment | A – Adequate |

| **Study** | **Viegas 1982a** |
|---|---|
| Methods | Allocation method not reported. |

**Characteristics of included studies** (*Continued*)

| | |
|---|---|
| Participants | 153 Asian women in Birmingham, UK < 20 weeks' gestation who appeared well-nourished based on their weight and height. |
| Interventions | Experimental: supplement of flavoured carbonated glucose drink providing 273 kcal energy (with 11% of energy as protein) plus vitamins from 18 to 38 weeks.<br>Control: supplement of flavoured carbonated water containing iron and vitamin C. |
| Outcomes | Gestational weight gain and birthweight, placental weight, maternal skinfolds and arm circumference. |
| Notes | 1) Designed as 3-arm trial, but group receiving supplement with 11% of energy provided as protein combined with energy-only group for this review.<br>2) No evidence that study women were undernourished.<br>3) No data presented on compliance or dietary substitution.<br>4) Results presented only in graphic form; extracted data are therefore approximate. |
| Allocation concealment | C – Inadequate |

| **Study** | **Viegas 1982b** |
|---|---|
| Methods | Allocation method not reported. |
| Participants | 130 Asian women in Birmingham, UK < 20 weeks' gestation (who appeared well-nourished (based on height and weight) prior to pregnancy, 45 of whom were later considered "nutritionally at risk" based on inadequate increase in triceps skinfolds between 18 and 28 weeks) stratified at 28 weeks according to increase in triceps skinfold during second trimester (<= 0.02 vs > 0.02 mm/week). |
| Interventions | Experimental: supplement of flavoured carbonated glucose drink + skim milk powder providing 425 kcal energy (with 10% of energy as protein), plus vitamins from 28 to 38 weeks.<br>Control: supplement of flavoured carbonated water containing iron and vitamin C. |
| Outcomes | Gestational weight gain, gestational age, birthweight, length, and head circumference, placental weight, and maternal skinfolds. |
| Notes | 1) Designed as 3-arm trial, but group receiving supplement with 10% of energy provided as protein combined with energy-only group for this review.<br>2) No data presented on compliance or dietary substitution.<br>3) Results for gestational weight gain presented only in graphic form; extracted data are therefore approximate.<br>4) Probable misprint in Table II: mean gestational age in supplemented (EnVi = energy plus vitamins) group assumed to be 39.2 weeks, rather than the 29.2 weeks indicated in the table.<br>5) Data on outcomes stratified according to increase in triceps skinfolds from 18-28 weeks. Because of harmful effect in those with normal skinfolds and no statement that threshold was established a priori, outcomes from both strata have been combined in review.<br>6) Data from intention-to-treat analysis extracted from graph; not presented in tabular form.<br>7) Probable misprint in gestational age for control group (adequate skinfold stratum) in Table II. |
| Allocation concealment | C – Inadequate |

GA: gestational age
IQ: intelligence quotient
IUGR: intrauterine growth retardation
IVGTT: intravenous glucose tolerance test
LBW: low birthweight
PIH: pregnancy-induced hypertension
SD: standard deviation
SEM: standard error of the mean
SES: socioeconomic status
SGA: small for gestational age
vs: versus

## Characteristics of excluded studies

| Study | Reason for exclusion |
|---|---|
| Adams 1978 | Large, differential losses to follow up. |
| Anderson 1995 | The nutritional advice studied does not relate to energy or protein intake, or both. |
| Clapp 1997 | Experimental intervention involved no change in energy or protein intake, but only in the type of carbohydrate in the diet. Moreover, the only outcomes studied were glycemic (blood glucose) responses to diet and exercise. |
| Dirige 1987 | Large, differential losses to follow up. |
| Ebbs 1941 | Very unequal study group sizes suggest biased allocation. |
| Fard 2004 | RCT of maternal dietary fat modification with no net supplementation of energy or protein. |
| Kaseb 2002 | Small (n = 53) cluster-allocated intervention without apparent randomization and only 2 study sites (clusters). |
| Lechtig 1975 | Despite the orginal RCT design, the reported results were based on observational analyses of the data. In one report of this trial (Delgado 1982), the results were indeed presented according to randomized treatment. This report was also excluded, however, because the analysis was based on individual women despite randomization by village, was limited to women with data on length of gestation, and showed evidence of major problems in validity of gestational age measurements. Stein 2003 was also based on the treatment allocation as randomized but suffered from huge losses to follow up (e.g., data were available on only 118 of the 1039 randomized for birthweight and only 90 for gestational age). Similarly, Webb 2005 examined long-term outcomes according to randomised treatment allocation but followed up only 450 (34%) of 1308 randomized women. |
| Luke 2001 | Not randomized or quasi-randomized trial. |
| Metcoff 1985 | Numbers of supplemented vs unsupplemented women analyzed suggests either deviation from the planned 2:1 randomization or differential losses to follow up. |
| Moses 2006 | RCT of diets with high vs low glycemic index, with no net supplementation of energy or protein. |
| Qureshi 1973 | The number of women originally allocated is not stated, and stillbirths and preterm births were excluded. |
| Tompkins 1954 | Very unequal study group sizes suggest biased allocation. |
| Tontisirin 1986 | The number of women originally allocated is not stated. In addition, the reported SDs for gestational weight gain are unrealistically small; they may represent SEMs. Finally, the tables (especially Table 4) contain many errors. |
| Woods 1995 | Small (n = 10) crossover trial of high- vs low-protein diet, but no pregnancy or offspring outcomes are analyzed. The only outcomes reported are renal hemodynamic responses to a meat meal. |

RCT: randomized controlled trial
vs: versus
SD: standard deviation
SEM: standard error of the mean

# ANALYSES

## Comparison 01. Nutritional advice during pregnancy

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Small-for-gestational age | 1 | 404 | Relative Risk (Fixed) 95% CI | 0.97 [0.45, 2.11] |
| 02 Preterm birth | 2 | 449 | Relative Risk (Fixed) 95% CI | 0.46 [0.21, 0.98] |
| 03 Pre-eclampsia | 1 | 136 | Relative Risk (Fixed) 95% CI | 0.89 [0.42, 1.88] |
| 04 Stillbirth | 1 | 431 | Relative Risk (Fixed) 95% CI | 0.37 [0.07, 1.90] |
| 05 Neonatal death | 1 | 448 | Relative Risk (Fixed) 95% CI | 1.28 [0.35, 4.72] |
| 06 Energy intake (kcal/day) | 3 | 342 | Weighted Mean Difference (Fixed) 95% CI | 105.61 [-18.94, 230.15] |
| 07 Protein intake (g/day) | 3 | 632 | Weighted Mean Difference (Random) 95% CI | 17.99 [-1.47, 37.45] |

| | | | | |
|---|---|---|---|---|
| 08 Total gestational weight gain (kg) | 2 | 233 | Weighted Mean Difference (Fixed) 95% CI | 0.83 [-0.24, 1.91] |
| 09 Birthweight (g) | 2 | 426 | Weighted Mean Difference (Random) 95% CI | 205.75 [-242.54, 654.03] |
| 10 Birth length (cm) | 1 | 399 | Weighted Mean Difference (Fixed) 95% CI | 0.17 [-0.72, 1.06] |
| 11 Birth head circumference (cm) | 1 | 389 | Weighted Mean Difference (Fixed) 95% CI | 0.99 [0.43, 1.55] |
| 12 Gestational age (week) | 1 | 399 | Weighted Mean Difference (Fixed) 95% CI | -0.10 [-0.48, 0.28] |

**Comparison 02. Balanced protein/energy supplementation in pregnancy**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Small-for-gestational age | 6 | 3396 | Relative Risk (Fixed) 95% CI | 0.68 [0.56, 0.84] |
| 02 Preterm birth | 5 | 2436 | Relative Risk (Fixed) 95% CI | 0.83 [0.65, 1.06] |
| 03 Pre-eclampsia | 3 | 516 | Relative Risk (Fixed) 95% CI | 1.20 [0.77, 1.89] |
| 04 Stillbirth | 4 | 2206 | Relative Risk (Fixed) 95% CI | 0.55 [0.31, 0.97] |
| 05 Neonatal death | 4 | 2206 | Relative Risk (Fixed) 95% CI | 0.62 [0.37, 1.05] |
| 06 Birthweight (g) | 14 | 4699 | Weighted Mean Difference (Random) 95% CI | 37.62 [-0.21, 75.45] |
| 07 Gestational age (week) | 7 | 2656 | Weighted Mean Difference (Fixed) 95% CI | -0.09 [-0.20, 0.03] |
| 08 Weekly gestational weight gain (g/week) | 10 | 2571 | Weighted Mean Difference (Random) 95% CI | 20.74 [1.46, 40.02] |
| 09 Birth length (cm) | 6 | 2679 | Weighted Mean Difference (Fixed) 95% CI | 0.10 [-0.06, 0.26] |
| 10 Birth head circumference (cm) | 6 | 2661 | Weighted Mean Difference (Random) 95% CI | 0.07 [-0.07, 0.20] |
| 11 Bayley mental score at 1 year | 1 | 411 | Weighted Mean Difference (Fixed) 95% CI | -0.74 [-1.95, 0.47] |
| 12 IQ at 5 years | 1 | 153 | Weighted Mean Difference (Fixed) 95% CI | 0.00 [-4.98, 4.98] |
| 13 Weight at 1 year (g) | 2 | 623 | Weighted Mean Difference (Fixed) 95% CI | 30.43 [-139.67, 200.53] |
| 14 Length at 1 year (cm) | 2 | 628 | Weighted Mean Difference (Fixed) 95% CI | 0.21 [-0.46, 0.88] |
| 15 Head circumference at 1 year (cm) | 2 | 627 | Weighted Mean Difference (Fixed) 95% CI | -0.13 [-0.35, 0.10] |
| 16 Maternal weight 4 weeks' postpartum (kg) | 1 | 354 | Weighted Mean Difference (Fixed) 95% CI | -0.90 [-1.92, 0.12] |
| 17 Duration of labor (hours) | 1 | 345 | Weighted Mean Difference (Fixed) 95% CI | -0.09 [-1.18, 1.00] |
| 18 Breast milk output at 2-3 months (g/day) | 1 | 55 | Weighted Mean Difference (Fixed) 95% CI | 6.00 [-57.96, 69.96] |

**Comparison 03. High protein supplementation in pregnancy**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Small-for-gestational age | 1 | 505 | Relative Risk (Fixed) 95% CI | 1.58 [1.03, 2.41] |
| 02 Preterm birth | 1 | 505 | Relative Risk (Fixed) 95% CI | 1.14 [0.83, 1.56] |
| 03 Stillbirth | 1 | 529 | Relative Risk (Fixed) 95% CI | 0.81 [0.31, 2.15] |
| 04 Neonatal death | 1 | 529 | Relative Risk (Fixed) 95% CI | 2.78 [0.75, 10.36] |
| 05 Weekly gestational weight gain (g/week) | 2 | 511 | Weighted Mean Difference (Fixed) 95% CI | 2.98 [-33.02, 38.98] |
| 06 Birthweight (g) | 2 | 529 | Weighted Mean Difference (Fixed) 95% CI | -58.37 [-146.23, 29.49] |
| 07 Weight at 1 year (g) | 1 | 409 | Weighted Mean Difference (Fixed) 95% CI | 61.00 [-184.60, 306.60] |
| 08 Length at 1 year (cm) | 1 | 412 | Weighted Mean Difference (Fixed) 95% CI | 0.20 [-0.38, 0.78] |
| 09 Head circumference at 1 year | 1 | 412 | Weighted Mean Difference (Fixed) 95% CI | 0.11 [-0.19, 0.41] |

| | | | | |
|---|---|---|---|---|
| 10 Bayley mental score at 1 year | 1 | 396 | Weighted Mean Difference (Fixed) 95% CI | 0.32 [-0.91, 1.55] |

**Comparison 04. Isocaloric balanced protein supplementation in pregnancy**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Small-for-gestational age | 1 | 782 | Relative Risk (Fixed) 95% CI | 1.35 [1.12, 1.61] |
| 02 Preterm birth | 1 | 782 | Relative Risk (Fixed) 95% CI | 1.05 [0.69, 1.60] |
| 03 Stillbirth | 1 | 782 | Relative Risk (Fixed) 95% CI | Not estimable |
| 04 Neonatal death | 1 | 782 | Relative Risk (Fixed) 95% CI | 0.50 [0.05, 5.49] |
| 05 Pre-eclampsia | 1 | 782 | Relative Risk (Fixed) 95% CI | 1.00 [0.57, 1.75] |
| 06 Birthweight (g) | 3 | 966 | Weighted Mean Difference (Random) 95% CI | 33.45 [-157.88, 224.77] |
| 07 Gestational age (wk) | 1 | 782 | Weighted Mean Difference (Fixed) 95% CI | -0.17 [-0.46, 0.12] |
| 08 Weekly gestational weight gain (g/week) | 3 | 966 | Weighted Mean Difference (Random) 95% CI | 51.68 [-75.05, 178.42] |
| 09 Birth length (cm) | 1 | 782 | Weighted Mean Difference (Fixed) 95% CI | 0.09 [-0.20, 0.38] |
| 10 Birth head circumference (cm) | 1 | 782 | Weighted Mean Difference (Fixed) 95% CI | -0.16 [-0.39, 0.07] |

**Comparison 05. Energy/protein restriction in pregnant women with high weight-for-height or weight gain**

| Outcome title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 01 Pre-eclampsia | 2 | 284 | Relative Risk (Fixed) 95% CI | 1.13 [0.59, 2.18] |
| 02 Pregnancy-induced hypertension | 3 | 384 | Relative Risk (Fixed) 95% CI | 0.97 [0.75, 1.26] |
| 03 Preterm birth | 1 | 182 | Relative Risk (Fixed) 95% CI | 0.50 [0.09, 2.66] |
| 04 Weekly gestational weight gain (g/wk) | 2 | 253 | Weighted Mean Difference (Random) 95% CI | -254.81 [-436.55, -73.06] |
| 05 Birthweight (g) | 2 | 282 | Weighted Mean Difference (Random) 95% CI | -217.93 [-664.73, 228.87] |
| 06 Birth length (cm) | 1 | 168 | Weighted Mean Difference (Fixed) 95% CI | -0.02 [-0.62, 0.58] |
| 07 Gestational age (week) | 1 | 172 | Weighted Mean Difference (Fixed) 95% CI | 0.25 [-0.17, 0.67] |

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Dietary Proteins [*administration & dosage]; *Energy Intake; Pregnancy Outcome; Randomized Controlled Trials; *Weight Gain

**MeSH check words**

Female; Humans; Pregnancy

## COVER SHEET

**Title** Energy and protein intake in pregnancy

**Authors** Kramer MS, Kakuma R

**Contribution of author(s)** M Kramer developed the five original separate reviews that have been combined in this updated amalgamation. R Kakuma carried out independent quality rating and data extraction of all included studies and helped revise the 'Table of included studies'.

**Issue protocol first published** 1997/2

| | |
|---|---|
| **Review first published** | 1997/2 |
| **Date of most recent amendment** | 30 January 2007 |
| **Date of most recent SUBSTANTIVE amendment** | 07 July 2003 |
| **What's New** | November 2006<br>New search conducted in November 2006 identified eight new reports to evaluate (Anderson 1995; Conlisk 2004; Fard 2004; Kaseb 2002; Moses 2006; Stein 2003; Webb 2005; Woods 1995), none of which were eligible for inclusion in the update. We have substantially updated the Methods of the review section. |
| **Date new studies sought but none found** | Information not supplied by author |
| **Date new studies found but not yet included/excluded** | Information not supplied by author |
| **Date new studies found and included/excluded** | 21 November 2006 |
| **Date authors' conclusions section amended** | Information not supplied by author |
| **Contact address** | Prof Michael Kramer<br>McGill University<br>Faculty of Medicine<br>1020 Pine Avenue West<br>Montreal<br>Quebec<br>H3A 1A2<br>CANADA<br>E-mail: michael.kramer@mcgill.ca<br>Tel: +1 514 3986261<br>Fax: +1 514 3984503 |
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## GRAPHS AND OTHER TABLES

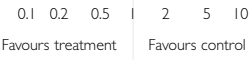
### Analysis 01.01. Comparison 01 Nutritional advice during pregnancy, Outcome 01 Small-for-gestational age

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 01 Small-for-gestational age

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Kafatos 1989 | 12/205 | 12/199 | | 100.0 | 0.97 [ 0.45, 2.11 ] |
| Total (95% CI) | 205 | 199 | | 100.0 | 0.97 [ 0.45, 2.11 ] |
| Total events: 12 (Treatment), 12 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.08 p=0.9 | | | | | |




### Analysis 01.02. Comparison 01 Nutritional advice during pregnancy, Outcome 02 Preterm birth

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 02 Preterm birth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Briley 2002 | 0/10 | 1/10 | | 7.7 | 0.33 [ 0.02, 7.32 ] |
| Kafatos 1989 | 9/228 | 17/201 | | 92.3 | 0.47 [ 0.21, 1.02 ] |
| Total (95% CI) | 238 | 211 | | 100.0 | 0.46 [ 0.21, 0.98 ] |
| Total events: 9 (Treatment), 18 (Control) | | | | | |
| Test for heterogeneity chi-square=0.04 df=1 p=0.84 $I^2$ =0.0% | | | | | |
| Test for overall effect z=2.02 p=0.04 | | | | | |

### Analysis 01.03. Comparison 01 Nutritional advice during pregnancy, Outcome 03 Pre-eclampsia

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 03 Pre-eclampsia

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Hankin 1962 | 17/96 | 8/40 | | 100.0 | 0.89 [ 0.42, 1.88 ] |
| Total (95% CI) | 96 | 40 | | 100.0 | 0.89 [ 0.42, 1.88 ] |
| Total events: 17 (Treatment), 8 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.32 p=0.8 | | | | | |


### Analysis 01.04. Comparison 01 Nutritional advice during pregnancy, Outcome 04 Stillbirth

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 04 Stillbirth

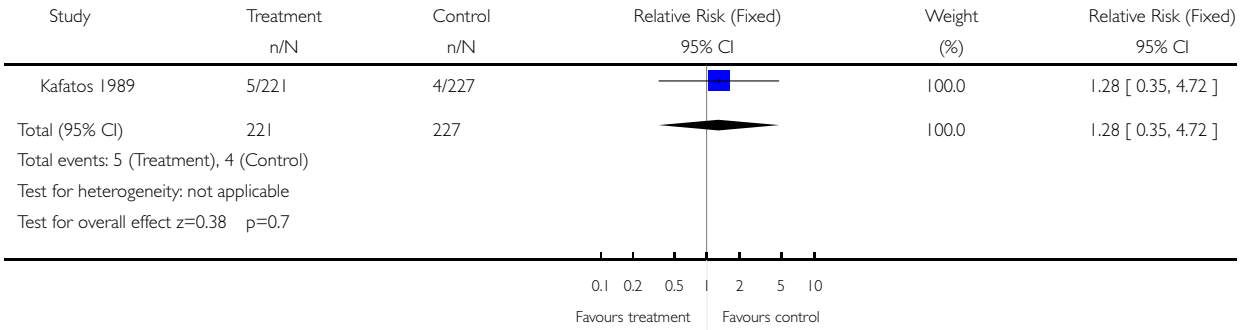
| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Kafatos 1989 | 2/223 | 5/208 | | 100.0 | 0.37 [ 0.07, 1.90 ] |
| Total (95% CI) | 223 | 208 | | 100.0 | 0.37 [ 0.07, 1.90 ] |
| Total events: 2 (Treatment), 5 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.19 p=0.2 | | | | | |

### Analysis 01.05. Comparison 01 Nutritional advice during pregnancy, Outcome 05 Neonatal death

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 05 Neonatal death

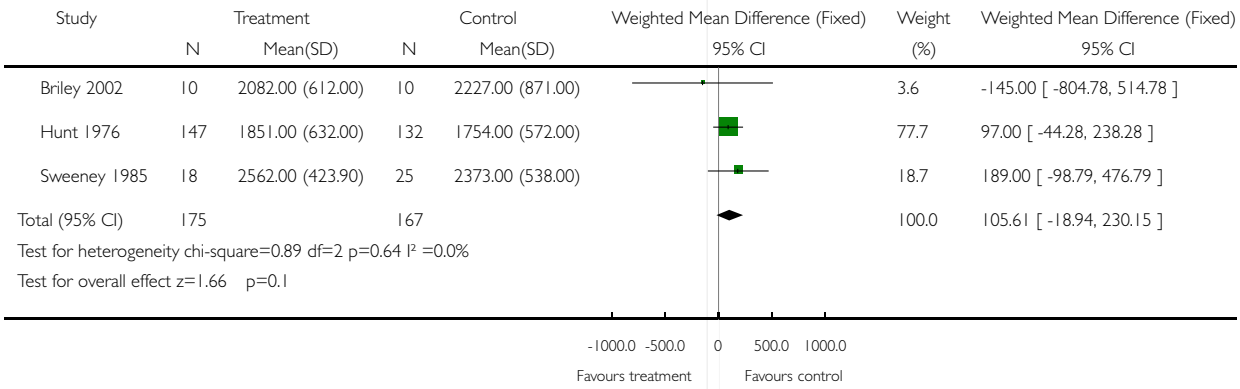



### Analysis 01.06. Comparison 01 Nutritional advice during pregnancy, Outcome 06 Energy intake (kcal/day)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 06 Energy intake (kcal/day)

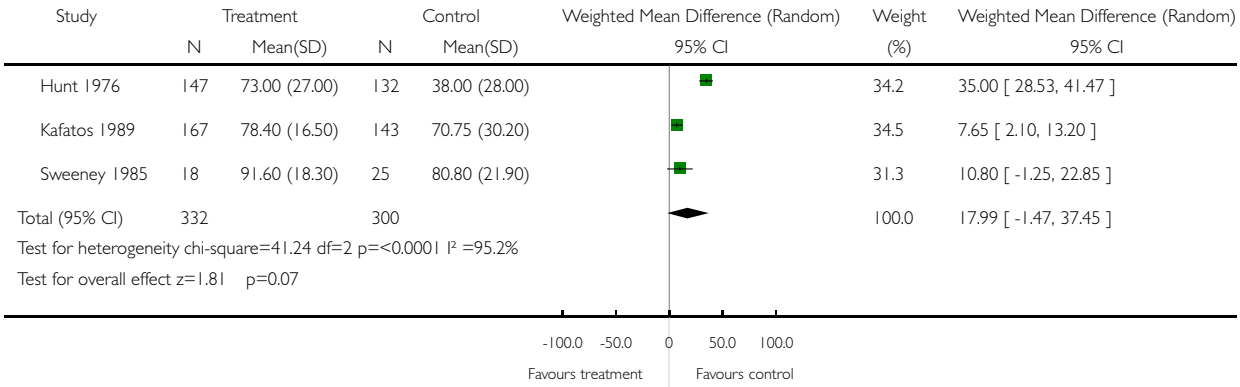


### Analysis 01.07. Comparison 01 Nutritional advice during pregnancy, Outcome 07 Protein intake (g/day)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 07 Protein intake (g/day)

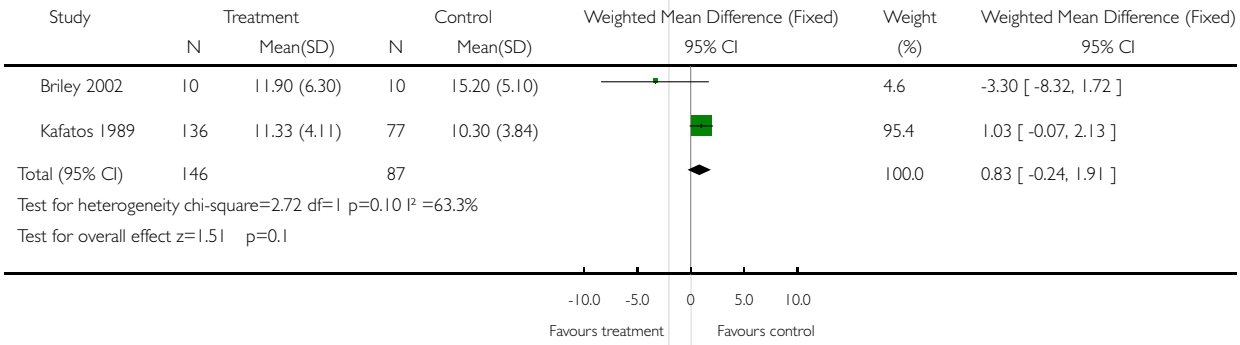



### Analysis 01.08. Comparison 01 Nutritional advice during pregnancy, Outcome 08 Total gestational weight gain (kg)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 08 Total gestational weight gain (kg)



### Analysis 01.09. Comparison 01 Nutritional advice during pregnancy, Outcome 09 Birthweight (g)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 09 Birthweight (g)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Briley 2002 | 10 | 3540.00 (400.00) | 10 | 3060.00 (500.00) | | 41.0 | 480.00 [ 83.14, 876.86 ] |
| Kafatos 1989 | 211 | 3391.00 (434.41) | 195 | 3376.00 (498.69) | | 59.0 | 15.00 [ -76.30, 106.30 ] |
| Total (95% CI) | 221 | | 205 | | | 100.0 | 205.75 [ -242.54, 654.03 ] |

Test for heterogeneity chi-square=5.01 df=1 p=0.03 $I^2$ =80.0%

Test for overall effect z=0.90 p=0.4


### Analysis 01.10. Comparison 01 Nutritional advice during pregnancy, Outcome 10 Birth length (cm)

Review: Energy and protein intake in pregnancy

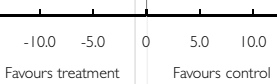
Comparison: 01 Nutritional advice during pregnancy

Outcome: 10 Birth length (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Kafatos 1989 | 206 | 50.09 (3.26) | 193 | 49.92 (5.46) | | 100.0 | 0.17 [ -0.72, 1.06 ] |
| Total (95% CI) | 206 | | 193 | | | 100.0 | 0.17 [ -0.72, 1.06 ] |

Test for heterogeneity: not applicable

Test for overall effect z=0.37 p=0.7




### Analysis 01.11. Comparison 01 Nutritional advice during pregnancy, Outcome 11 Birth head circumference (cm)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 11 Birth head circumference (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Kafatos 1989 | 197 | 34.38 (2.87) | 192 | 33.39 (2.79) | | 100.0 | 0.99 [ 0.43, 1.55 ] |
| Total (95% CI) | 197 | | 192 | | | 100.0 | 0.99 [ 0.43, 1.55 ] |

Test for heterogeneity: not applicable

Test for overall effect z=3.45 p=0.0006

### Analysis 01.12. Comparison 01 Nutritional advice during pregnancy, Outcome 12 Gestational age (week)

Review: Energy and protein intake in pregnancy

Comparison: 01 Nutritional advice during pregnancy

Outcome: 12 Gestational age (week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Kafatos 1989 | 205 | 39.60 (1.63) | 194 | 39.70 (2.19) | | 100.0 | -0.10 [ -0.48, 0.28 ] |
| Total (95% CI) | 205 | | 194 | | | 100.0 | -0.10 [ -0.48, 0.28 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.52 p=0.6 | | | | | | | |


### Analysis 02.01. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 01 Small-for-gestational age

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 01 Small-for-gestational age

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Blackwell 1973 | 6/94 | 10/88 | | 5.1 | 0.56 [ 0.21, 1.48 ] |
| Ceesay 1997 | 69/620 | 94/553 | | 49.5 | 0.65 [ 0.49, 0.87 ] |
| Elwood 1981 | 25/591 | 27/562 | | 13.8 | 0.88 [ 0.52, 1.50 ] |
| Girija 1984 | 0/10 | 5/10 | | 2.7 | 0.09 [ 0.01, 1.45 ] |
| Mora 1978 | 12/177 | 14/162 | | 7.3 | 0.78 [ 0.37, 1.65 ] |
| Rush 1980 | 30/265 | 43/264 | | 21.5 | 0.70 [ 0.45, 1.07 ] |
| Total (95% CI) | 1757 | 1639 | | 100.0 | 0.68 [ 0.56, 0.84 ] |
| Total events: 142 (Treatment), 193 (Control) | | | | | |
| Test for heterogeneity chi-square=3.29 df=5 p=0.66 $I^2$ =0.0% | | | | | |
| Test for overall effect z=3.66 p=0.0003 | | | | | |

### Analysis 02.02. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 02 Preterm birth

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 02 Preterm birth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Blackwell 1973 | 3/94 | 6/88 | | 5.3 | 0.47 [ 0.12, 1.81 ] |
| Campbell Brown 1983 | 7/97 | 8/98 | | 6.8 | 0.88 [ 0.33, 2.34 ] |
| Elwood 1981 | 9/557 | 10/539 | | 8.7 | 0.87 [ 0.36, 2.13 ] |
| Mora 1978 | 22/221 | 25/222 | | 21.3 | 0.88 [ 0.51, 1.52 ] |
| Rush 1980 | 56/256 | 69/264 | | 58.0 | 0.84 [ 0.62, 1.14 ] |
| Total (95% CI) | 1225 | 1211 | | 100.0 | 0.83 [ 0.65, 1.06 ] |
| Total events: 97 (Treatment), 118 (Control) | | | | | |
| Test for heterogeneity chi-square=0.77 df=4 p=0.94 I² =0.0% | | | | | |
| Test for overall effect z=1.46 p=0.1 | | | | | |

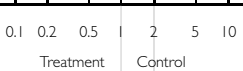

### Analysis 02.03. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 03 Pre-eclampsia

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 03 Pre-eclampsia

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| × Girija 1984 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Mora 1978 | 25/221 | 17/222 | | 60.2 | 1.48 [ 0.82, 2.66 ] |
| Ross 1938 | 9/27 | 11/26 | | 39.8 | 0.79 [ 0.39, 1.58 ] |
| Total (95% CI) | 258 | 258 | | 100.0 | 1.20 [ 0.77, 1.89 ] |
| Total events: 34 (Treatment), 28 (Control) | | | | | |
| Test for heterogeneity chi-square=1.89 df=1 p=0.17 I² =47.0% | | | | | |
| Test for overall effect z=0.80 p=0.4 | | | | | |



### Analysis 02.04. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 04 Stillbirth

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 04 Stillbirth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Ceesay 1997 | 7/652 | 13/545 | | 44.2 | 0.45 [ 0.18, 1.12 ] |
| × Girija 1984 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Mora 1978 | 2/221 | 8/222 | | 24.9 | 0.25 [ 0.05, 1.17 ] |
| Rush 1980 | 9/270 | 10/276 | | 30.9 | 0.92 [ 0.38, 2.23 ] |
| Total (95% CI) | 1153 | 1053 | | 100.0 | 0.55 [ 0.31, 0.97 ] |
| Total events: 18 (Treatment), 31 (Control) | | | | | |
| Test for heterogeneity chi-square=2.49 df=2 p=0.29 $I^2$ =19.6% | | | | | |
| Test for overall effect z=2.08 p=0.04 | | | | | |


### Analysis 02.05. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 05 Neonatal death

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 05 Neonatal death

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Ceesay 1997 | 15/652 | 21/545 | | 65.7 | 0.60 [ 0.31, 1.15 ] |
| × Girija 1984 | 0/10 | 0/10 | | 0.0 | Not estimable |
| Mora 1978 | 5/221 | 9/222 | | 25.8 | 0.56 [ 0.19, 1.64 ] |
| Rush 1980 | 3/270 | 3/276 | | 8.5 | 1.02 [ 0.21, 5.02 ] |
| Total (95% CI) | 1153 | 1053 | | 100.0 | 0.62 [ 0.37, 1.05 ] |
| Total events: 23 (Treatment), 33 (Control) | | | | | |
| Test for heterogeneity chi-square=0.43 df=2 p=0.81 $I^2$ =0.0% | | | | | |
| Test for overall effect z=1.77 p=0.08 | | | | | |

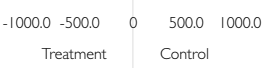
## Analysis 02.06. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 06 Birthweight (g)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 06 Birthweight (g)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| 01 Undernourished women | | | | | | | |
| Atton 1990 | 87 | 3130.00 (374.00) | 61 | 3190.00 (402.00) | | 6.1 | -60.00 [ -187.88, 67.88 ] |
| Blackwell 1973 | 55 | 3082.13 (400.83) | 55 | 2941.93 (306.74) | | 5.7 | 140.20 [ 6.81, 273.59 ] |
| Campbell Brown 1983 | 90 | 3032.00 (372.00) | 90 | 2995.00 (395.00) | | 7.2 | 37.00 [ -75.10, 149.10 ] |
| Ceesay 1997 | 620 | 2966.00 (422.00) | 553 | 2860.00 (427.00) | | 14.9 | 106.00 [ 57.32, 154.68 ] |
| Girija 1984 | 10 | 2939.00 (376.00) | 10 | 2676.00 (451.00) | | 1.0 | 263.00 [ -100.93, 626.93 ] |
| Kardjati 1988 | 258 | 2908.00 (397.00) | 252 | 2948.00 (392.00) | | 12.0 | -40.00 [ -108.48, 28.48 ] |
| Mora 1978 | 207 | 2978.00 (377.00) | 200 | 2927.00 (392.00) | | 11.2 | 51.00 [ -23.76, 125.76 ] |
| Rush 1980 | 256 | 3011.00 (508.00) | 264 | 2970.00 (535.00) | | 9.4 | 41.00 [ -48.65, 130.65 ] |
| Viegas 1982b | 31 | 3184.00 (540.00) | 14 | 3027.00 (255.00) | | 2.3 | 157.00 [ -75.33, 389.33 ] |
| Subtotal (95% CI) | 1614 | | 1499 | | | 69.9 | 49.40 [ -1.98, 100.78 ] |
| Test for heterogeneity chi-square=18.48 df=8 p=0.02 $I^2$ =56.7% | | | | | | | |
| Test for overall effect z=1.88 p=0.06 | | | | | | | |
| 02 Adequately nourished women | | | | | | | |
| Blackwell 1973 | 57 | 3184.00 (335.00) | 56 | 3189.93 (333.44) | | 6.4 | -5.93 [ -129.18, 117.32 ] |
| Elwood 1981 | 591 | 3378.00 (519.00) | 562 | 3325.00 (498.00) | | 13.4 | 53.00 [ -5.70, 111.70 ] |
| Ross 1985 | 62 | 3229.00 (432.50) | 33 | 3171.00 (483.00) | | 3.1 | 58.00 [ -138.84, 254.84 ] |
| Viegas 1982a | 97 | 3028.00 (431.00) | 45 | 3060.00 (472.00) | | 4.3 | -32.00 [ -194.40, 130.40 ] |
| Viegas 1982b | 56 | 3115.00 (454.00) | 27 | 3233.00 (433.00) | | 3.0 | -118.00 [ -320.03, 84.03 ] |
| Subtotal (95% CI) | 863 | | 723 | | | 30.1 | 27.87 [ -19.57, 75.32 ] |
| Test for heterogeneity chi-square=3.61 df=4 p=0.46 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=1.15 p=0.2 | | | | | | | |
| Total (95% CI) | 2477 | | 2222 | | | 100.0 | 37.62 [ -0.21, 75.45 ] |
| Test for heterogeneity chi-square=22.91 df=13 p=0.04 $I^2$ =43.3% | | | | | | | |
| Test for overall effect z=1.95 p=0.05 | | | | | | | |



### Analysis 02.07. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 07 Gestational age (week)

Review: Energy and protein intake in pregnancy

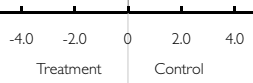
Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 07 Gestational age (week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Atton 1990 | 87 | 39.09 (1.40) | 61 | 39.50 (1.10) | | 7.7 | -0.41 [ -0.81, -0.01 ] |
| Campbell Brown 1983 | 90 | 39.70 (0.98) | 90 | 39.60 (1.06) | | 14.1 | 0.10 [ -0.20, 0.40 ] |
| Ceesay 1997 | 359 | 39.91 (1.36) | 316 | 40.01 (1.37) | | 29.5 | -0.10 [ -0.31, 0.11 ] |
| Elwood 1981 | 557 | 40.00 (1.50) | 539 | 40.10 (1.40) | | 42.6 | -0.10 [ -0.27, 0.07 ] |
| Girija 1984 | 10 | 36.50 (1.95) | 10 | 36.80 (1.86) | | 0.5 | -0.30 [ -1.97, 1.37 ] |
| Mora 1978 | 221 | 39.40 (2.50) | 222 | 39.30 (2.90) | | 4.9 | 0.10 [ -0.40, 0.60 ] |
| Ross 1985 | 62 | 38.90 (2.50) | 32 | 38.90 (3.50) | | 0.7 | 0.00 [ -1.36, 1.36 ] |
| Total (95% CI) | 1386 | | 1270 | | | 100.0 | -0.09 [ -0.20, 0.03 ] |

Test for heterogeneity chi-square=4.62 df=6 p=0.59 $I^2$ =0.0%

Test for overall effect z=1.50 p=0.1



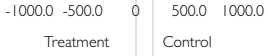

### Analysis 02.08. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 08 Weekly gestational weight gain (g/week)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 08 Weekly gestational weight gain (g/week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Blackwell 1973 | 107 | 193.00 (71.00) | 105 | 198.00 (64.00) | | 19.1 | -5.00 [ -23.19, 13.19 ] |
| Campbell Brown 1983 | 90 | 403.00 (168.00) | 90 | 359.00 (191.00) | | 8.5 | 44.00 [ -8.55, 96.55 ] |
| Ceesay 1997 | 304 | 283.00 (158.00) | 266 | 271.33 (162.67) | | 16.1 | 11.67 [ -14.74, 38.08 ] |
| Girija 1984 | 10 | 325.00 (100.00) | 10 | 329.20 (175.00) | | 2.2 | -4.20 [ -129.12, 120.72 ] |
| Kardjati 1988 | 174 | 168.30 (146.70) | 180 | 158.30 (145.80) | | 14.6 | 10.00 [ -20.48, 40.48 ] |
| Mora 1978 | 190 | 322.51 (157.63) | 179 | 259.99 (125.96) | | 15.1 | 62.52 [ 33.49, 91.55 ] |
| Ross 1985 | 62 | 433.50 (203.50) | 33 | 465.61 (201.06) | | 4.2 | -32.11 [ -117.38, 53.16 ] |
| Rush 1980 | 246 | 431.30 (199.80) | 255 | 413.10 (204.30) | | 13.0 | 18.20 [ -17.19, 53.59 ] |
| Viegas 1982a | 97 | 411.00 (220.40) | 45 | 335.00 (258.00) | | 4.0 | 76.00 [ -11.21, 163.21 ] |

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| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Viegas 1982b | 87 | 437.60 (291.00) | 41 | 402.00 (247.00) | | 3.4 | 35.60 [ -61.64, 132.84 ] |
| Total (95% CI) | 1367 | | 1204 | | | 100.0 | 20.74 [ 1.46, 40.02 ] |
| Test for heterogeneity chi-square=19.62 df=9 p=0.02 $I^2$ =54.1% | | | | | | | |
| Test for overall effect z=2.11 p=0.03 | | | | | | | |

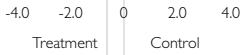

## Analysis 02.09. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 09 Birth length (cm)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 09 Birth length (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Atton 1990 | 87 | 50.59 (2.38) | 61 | 50.60 (2.30) | | 4.5 | -0.01 [ -0.77, 0.75 ] |
| Blackwell 1973 | 108 | 49.23 (1.90) | 105 | 49.09 (1.79) | | 10.7 | 0.14 [ -0.36, 0.64 ] |
| Campbell Brown 1983 | 90 | 48.50 (1.87) | 90 | 48.20 (1.83) | | 9.0 | 0.30 [ -0.24, 0.84 ] |
| Ceesay 1997 | 540 | 49.30 (2.30) | 481 | 49.30 (2.20) | | 34.4 | 0.00 [ -0.28, 0.28 ] |
| Elwood 1981 | 562 | 51.80 (2.20) | 535 | 51.70 (2.10) | | 40.6 | 0.10 [ -0.15, 0.35 ] |
| Girija 1984 | 10 | 47.70 (1.70) | 10 | 45.90 (2.30) | | 0.8 | 1.80 [ 0.03, 3.57 ] |
| Total (95% CI) | 1397 | | 1282 | | | 100.0 | 0.10 [ -0.06, 0.26 ] |
| Test for heterogeneity chi-square=4.67 df=5 p=0.46 $I^2$ =0.0% | | | | | | | |
| Test for overall effect z=1.17 p=0.2 | | | | | | | |



## Analysis 02.10. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 10 Birth head circumference (cm)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 10 Birth head circumference (cm)

| Study | Treatment | | Control | | Weighted Mean Difference (Random) | Weight | Weighted Mean Difference (Random) |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | 95% CI | (%) | 95% CI |
| Atton 1990 | 87 | 34.07 (1.15) | 61 | 34.40 (1.50) | | 7.8 | -0.33 [ -0.78, 0.12 ] |
| Blackwell 1973 | 108 | 33.43 (1.10) | 105 | 33.35 (1.07) | | 15.8 | 0.08 [ -0.21, 0.37 ] |
| Campbell Brown 1983 | 90 | 34.30 (1.33) | 90 | 34.10 (1.26) | | 10.4 | 0.20 [ -0.18, 0.58 ] |
| Ceesay 1997 | 533 | 33.60 (1.40) | 475 | 33.40 (1.40) | | 31.3 | 0.20 [ 0.03, 0.37 ] |
| Elwood 1981 | 561 | 35.90 (1.40) | 536 | 35.90 (1.30) | | 34.0 | 0.00 [ -0.16, 0.16 ] |
| Girija 1984 | 6 | 37.10 (1.60) | 9 | 37.50 (1.40) | | 0.7 | -0.40 [ -1.97, 1.17 ] |
| Total (95% CI) | 1385 | | 1276 | | | 100.0 | 0.07 [ -0.07, 0.20 ] |

Test for heterogeneity chi-square=6.77 df=5 p=0.24 $I^2$ =26.1%

Test for overall effect z=1.00 p=0.3


## Analysis 02.11. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 11 Bayley mental score at 1 year

Review: Energy and protein intake in pregnancy

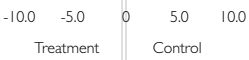
Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 11 Bayley mental score at 1 year

| Study | Treatment | | Control | | Weighted Mean Difference (Fixed) | Weight | Weighted Mean Difference (Fixed) |
|---|---|---|---|---|---|---|---|
| | N | Mean(SD) | N | Mean(SD) | 95% CI | (%) | 95% CI |
| Rush 1980 | 197 | 98.65 (6.23) | 214 | 99.39 (6.23) | | 100.0 | -0.74 [ -1.95, 0.47 ] |
| Total (95% CI) | 197 | | 214 | | | 100.0 | -0.74 [ -1.95, 0.47 ] |

Test for heterogeneity: not applicable

Test for overall effect z=1.20 p=0.2

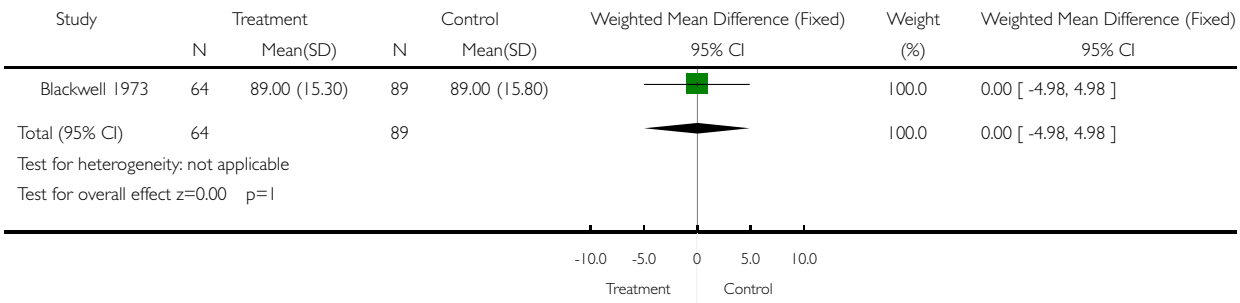


### Analysis 02.12. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 12 IQ at 5 years

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 12 IQ at 5 years

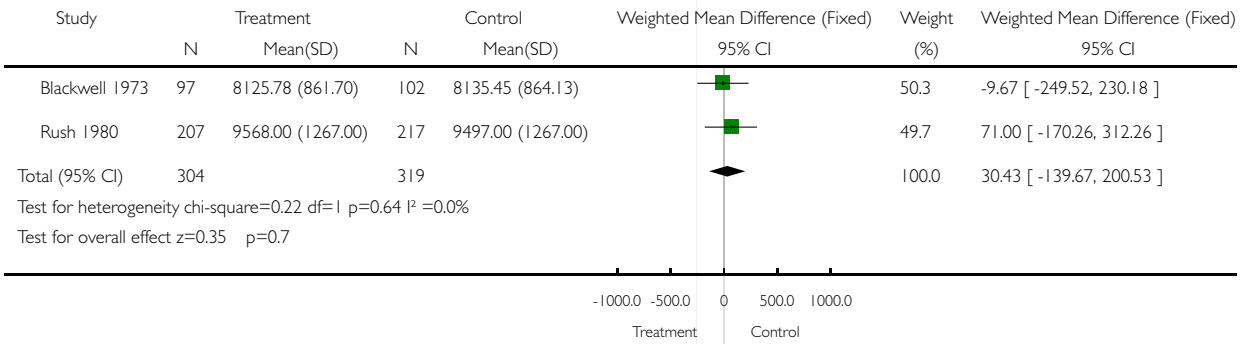



### Analysis 02.13. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 13 Weight at 1 year (g)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 13 Weight at 1 year (g)



## Analysis 02.14. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 14 Length at 1 year (cm)

Review: Energy and protein intake in pregnancy

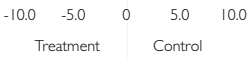
Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 14 Length at 1 year (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Blackwell 1973 | 98 | 71.50 (2.47) | 102 | 71.29 (2.39) | | 98.6 | 0.21 [ -0.46, 0.88 ] |
| Rush 1980 | 208 | 74.70 (30.00) | 220 | 74.70 (30.00) | | 1.4 | 0.00 [ -5.69, 5.69 ] |
| Total (95% CI) | 306 | | 322 | | | 100.0 | 0.21 [ -0.46, 0.88 ] |

Test for heterogeneity chi-square=0.01 df=1 p=0.94 $I^2$ =0.0%

Test for overall effect z=0.61 p=0.5




## Analysis 02.15. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 15 Head circumference at 1 year (cm)

Review: Energy and protein intake in pregnancy

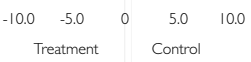
Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 15 Head circumference at 1 year (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Blackwell 1973 | 98 | 44.56 (1.35) | 102 | 44.79 (1.28) | | 38.8 | -0.23 [ -0.59, 0.13 ] |
| Rush 1980 | 208 | 45.97 (1.53) | 219 | 46.03 (1.53) | | 61.2 | -0.06 [ -0.35, 0.23 ] |
| Total (95% CI) | 306 | | 321 | | | 100.0 | -0.13 [ -0.35, 0.10 ] |

Test for heterogeneity chi-square=0.51 df=1 p=0.47 $I^2$ =0.0%

Test for overall effect z=1.09 p=0.3



### Analysis 02.16. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 16 Maternal weight 4 weeks' postpartum (kg)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 16 Maternal weight 4 weeks' postpartum (kg)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Kardjati 1988 | 176 | 43.20 (4.47) | 178 | 44.10 (5.30) | | 100.0 | -0.90 [ -1.92, 0.12 ] |
| Total (95% CI) | 176 | | 178 | | | 100.0 | -0.90 [ -1.92, 0.12 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.73 p=0.08 | | | | | | | |


### Analysis 02.17. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 17 Duration of labor (hours)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 17 Duration of labor (hours)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Mora 1978 | 184 | 6.22 (5.63) | 161 | 6.31 (4.73) | | 100.0 | -0.09 [ -1.18, 1.00 ] |
| Total (95% CI) | 184 | | 161 | | | 100.0 | -0.09 [ -1.18, 1.00 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.16 p=0.9 | | | | | | | |


### Analysis 02.18. Comparison 02 Balanced protein/energy supplementation in pregnancy, Outcome 18 Breast milk output at 2-3 months (g/day)

Review: Energy and protein intake in pregnancy

Comparison: 02 Balanced protein/energy supplementation in pregnancy

Outcome: 18 Breast milk output at 2-3 months (g/day)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Kardjati 1988 | 29 | 708.00 (128.00) | 26 | 702.00 (114.00) | | 100.0 | 6.00 [ -57.96, 69.96 ] |
| Total (95% CI) | 29 | | 26 | | | 100.0 | 6.00 [ -57.96, 69.96 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.18 p=0.9 | | | | | | | |

### Analysis 03.01. Comparison 03 High protein supplementation in pregnancy, Outcome 01 Small-for-gestational age

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 01 Small-for-gestational age

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Rush 1980 | 46/249 | 30/256 | | 100.0 | 1.58 [ 1.03, 2.41 ] |
| Total (95% CI) | 249 | 256 | | 100.0 | 1.58 [ 1.03, 2.41 ] |
| Total events: 46 (Treatment), 30 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=2.10 p=0.04 | | | | | |

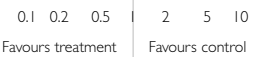

### Analysis 03.02. Comparison 03 High protein supplementation in pregnancy, Outcome 02 Preterm birth

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 02 Preterm birth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Rush 1980 | 62/249 | 56/256 | | 100.0 | 1.14 [ 0.83, 1.56 ] |
| Total (95% CI) | 249 | 256 | | 100.0 | 1.14 [ 0.83, 1.56 ] |
| Total events: 62 (Treatment), 56 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.80 p=0.4 | | | | | |



### Analysis 03.03. Comparison 03 High protein supplementation in pregnancy, Outcome 03 Stillbirth

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 03 Stillbirth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Rush 1980 | 7/259 | 9/270 | | 100.0 | 0.81 [ 0.31, 2.15 ] |
| Total (95% CI) | 259 | 270 | | 100.0 | 0.81 [ 0.31, 2.15 ] |
| Total events: 7 (Treatment), 9 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.42 p=0.7 | | | | | |

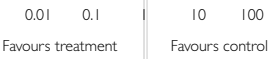

### Analysis 03.04. Comparison 03 High protein supplementation in pregnancy, Outcome 04 Neonatal death

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 04 Neonatal death

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Rush 1980 | 8/259 | 3/270 | | 100.0 | 2.78 [ 0.75, 10.36 ] |
| Total (95% CI) | 259 | 270 | | 100.0 | 2.78 [ 0.75, 10.36 ] |
| Total events: 8 (Treatment), 3 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.52 p=0.1 | | | | | |



### Analysis 03.05. Comparison 03 High protein supplementation in pregnancy, Outcome 05 Weekly gestational weight gain (g/week)

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 05 Weekly gestational weight gain (g/week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Iyengar 1967 | 12 | 307.50 (166.28) | 13 | 317.50 (109.07) | | 10.5 | -10.00 [ -121.20, 101.20 ] |
| Rush 1980 | 240 | 435.80 (227.00) | 246 | 431.30 (199.80) | | 89.5 | 4.50 [ -33.55, 42.55 ] |
| Total (95% CI) | 252 | | 259 | | | 100.0 | 2.98 [ -33.02, 38.98 ] |

Test for heterogeneity chi-square=0.06 df=1 p=0.81 $I^2$ =0.0%

Test for overall effect z=0.16 p=0.9


### Analysis 03.06. Comparison 03 High protein supplementation in pregnancy, Outcome 06 Birthweight (g)

Review: Energy and protein intake in pregnancy

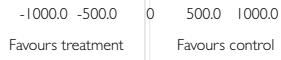
Comparison: 03 High protein supplementation in pregnancy

Outcome: 06 Birthweight (g)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Iyengar 1967 | 12 | 3028.00 (193.99) | 13 | 3028.00 (299.26) | | 20.0 | 0.00 [ -196.24, 196.24 ] |
| Rush 1980 | 248 | 2938.00 (611.00) | 256 | 3011.00 (508.00) | | 80.0 | -73.00 [ -171.26, 25.26 ] |
| Total (95% CI) | 260 | | 269 | | | 100.0 | -58.37 [ -146.23, 29.49 ] |

Test for heterogeneity chi-square=0.43 df=1 p=0.51 $I^2$ =0.0%

Test for overall effect z=1.30 p=0.2

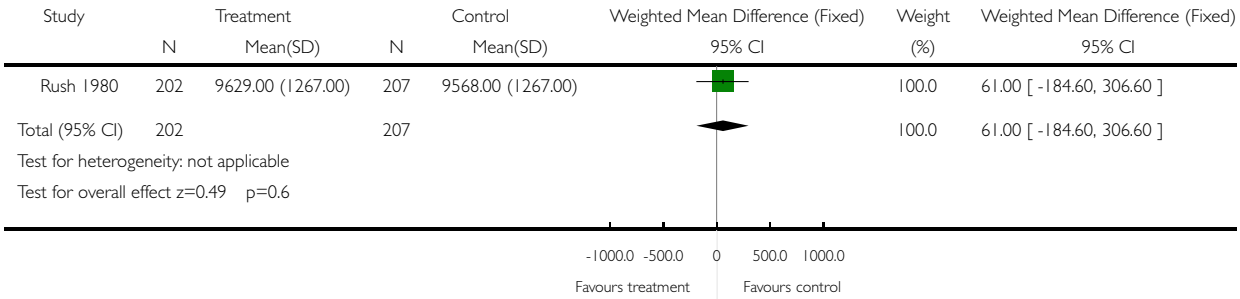


### Analysis 03.07. Comparison 03 High protein supplementation in pregnancy, Outcome 07 Weight at 1 year (g)

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 07 Weight at 1 year (g)

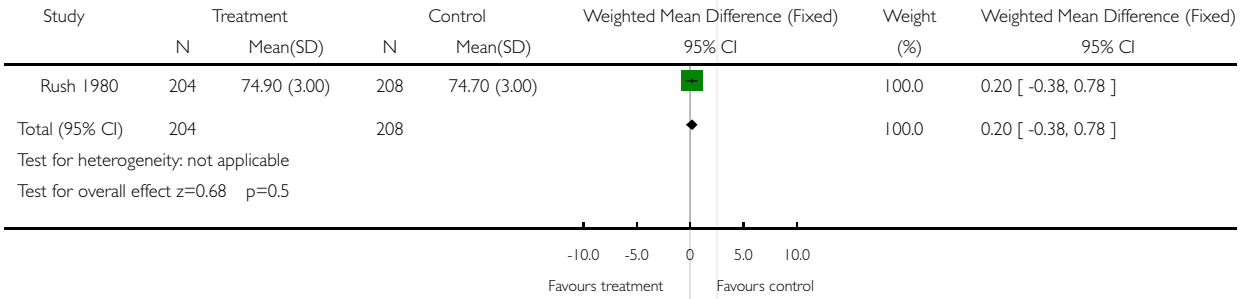



### Analysis 03.08. Comparison 03 High protein supplementation in pregnancy, Outcome 08 Length at 1 year (cm)

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 08 Length at 1 year (cm)

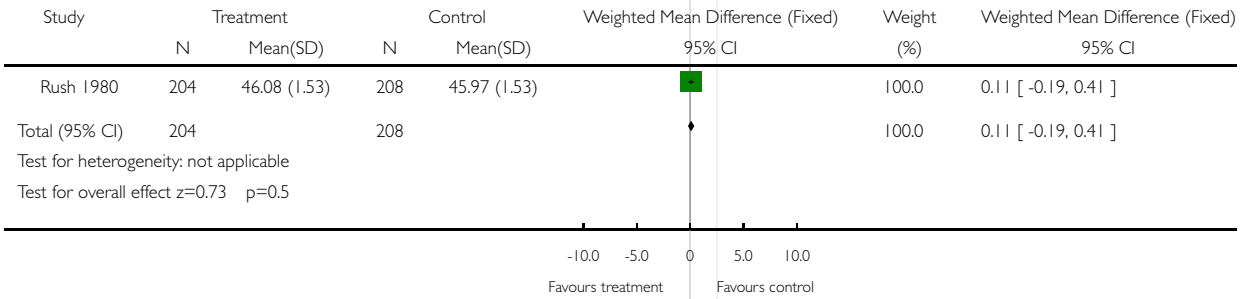



### Analysis 03.09. Comparison 03 High protein supplementation in pregnancy, Outcome 09 Head circumference at 1 year

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 09 Head circumference at 1 year

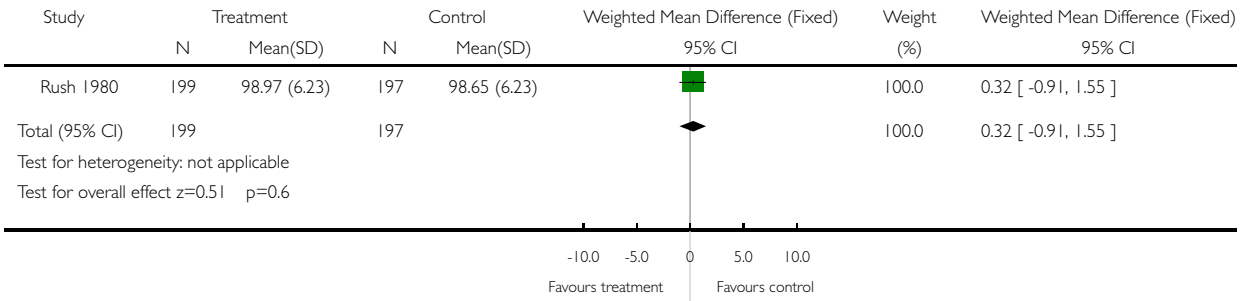


## Analysis 03.10. Comparison 03 High protein supplementation in pregnancy, Outcome 10 Bayley mental score at 1 year

Review: Energy and protein intake in pregnancy

Comparison: 03 High protein supplementation in pregnancy

Outcome: 10 Bayley mental score at 1 year

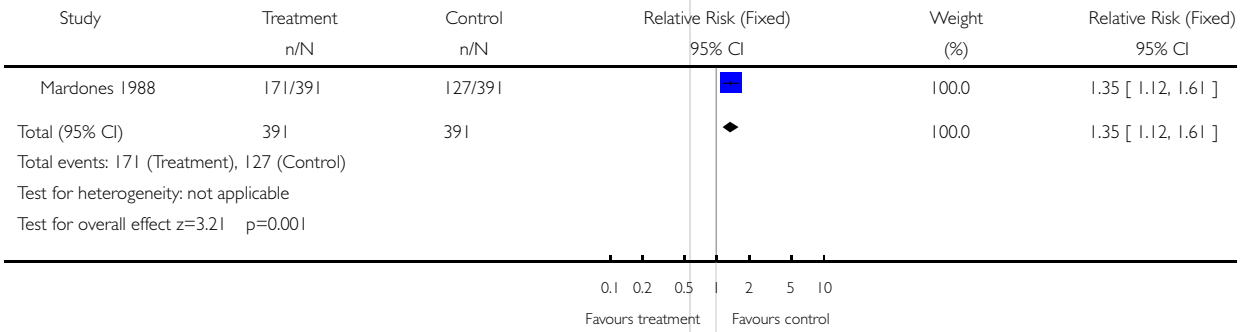



## Analysis 04.01. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 01 Small-for-gestational age

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 01 Small-for-gestational age



### Analysis 04.02. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 02 Preterm birth

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 02 Preterm birth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Mardones 1988 | 40/391 | 38/391 | | 100.0 | 1.05 [ 0.69, 1.60 ] |
| Total (95% CI) | 391 | 391 | | 100.0 | 1.05 [ 0.69, 1.60 ] |
| Total events: 40 (Treatment), 38 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.24 p=0.8 | | | | | |


### Analysis 04.03. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 03 Stillbirth

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 03 Stillbirth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| × Mardones 1988 | 0/391 | 0/391 | | 0.0 | Not estimable |
| Total (95% CI) | 391 | 391 | | 0.0 | Not estimable |
| Total events: 0 (Treatment), 0 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect: not applicable | | | | | |

### Analysis 04.04. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 04 Neonatal death

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 04 Neonatal death

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Mardones 1988 | 1/391 | 2/391 | | 100.0 | 0.50 [ 0.05, 5.49 ] |
| Total (95% CI) | 391 | 391 | | 100.0 | 0.50 [ 0.05, 5.49 ] |
| Total events: 1 (Treatment), 2 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.57 p=0.6 | | | | | |


### Analysis 04.05. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 05 Pre-eclampsia

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 05 Pre-eclampsia

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Mardones 1988 | 23/391 | 23/391 | | 100.0 | 1.00 [ 0.57, 1.75 ] |
| Total (95% CI) | 391 | 391 | | 100.0 | 1.00 [ 0.57, 1.75 ] |
| Total events: 23 (Treatment), 23 (Control) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.00 p=1 | | | | | |

### Analysis 04.06. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 06 Birthweight (g)

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 06 Birthweight (g)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Mardones 1988 | 391 | 3105.00 (495.40) | 391 | 3178.30 (483.80) | | 40.0 | -73.30 [ -141.94, -4.66 ] |
| Viegas 1982a | 47 | 3000.00 (417.00) | 50 | 3055.00 (444.00) | | 31.5 | -55.00 [ -226.34, 116.34 ] |
| Viegas 1982b | 44 | 3415.00 (471.00) | 43 | 3134.00 (499.00) | | 28.5 | 281.00 [ 77.01, 484.99 ] |
| Total (95% CI) | 482 | | 484 | | | 100.0 | 33.45 [ -157.88, 224.77 ] |

Test for heterogeneity chi-square=10.45 df=2 p=0.005 $I^2$ =80.9%

Test for overall effect z=0.34 p=0.7


### Analysis 04.07. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 07 Gestational age (wk)

Review: Energy and protein intake in pregnancy

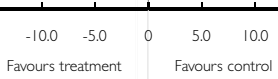
Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 07 Gestational age (wk)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Mardones 1988 | 391 | 39.08 (2.20) | 391 | 39.25 (1.89) | | 100.0 | -0.17 [ -0.46, 0.12 ] |
| Total (95% CI) | 391 | | 391 | | | 100.0 | -0.17 [ -0.46, 0.12 ] |

Test for heterogeneity: not applicable

Test for overall effect z=1.16 p=0.2



### Analysis 04.08. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 08 Weekly gestational weight gain (g/week)

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 08 Weekly gestational weight gain (g/week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Mardones 1988 | 391 | 452.40 (208.00) | 391 | 491.60 (186.00) | | 38.4 | -39.20 [ -66.86, -11.54 ] |
| Viegas 1982a | 47 | 419.50 (226.20) | 50 | 403.00 (214.90) | | 32.9 | 16.50 [ -71.42, 104.42 ] |
| Viegas 1982b | 44 | 494.00 (298.50) | 43 | 280.00 (284.70) | | 28.6 | 214.00 [ 91.44, 336.56 ] |
| Total (95% CI) | 482 | | 484 | | | 100.0 | 51.68 [ -75.05, 178.42 ] |

Test for heterogeneity chi-square=16.46 df=2 p=0.0003 $I^2$ =87.8%

Test for overall effect z=0.80 p=0.4


### Analysis 04.09. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 09 Birth length (cm)

Review: Energy and protein intake in pregnancy

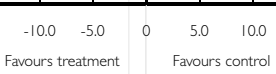
Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 09 Birth length (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Mardones 1988 | 391 | 49.17 (2.14) | 391 | 49.08 (1.97) | | 100.0 | 0.09 [ -0.20, 0.38 ] |
| Total (95% CI) | 391 | | 391 | | | 100.0 | 0.09 [ -0.20, 0.38 ] |

Test for heterogeneity: not applicable

Test for overall effect z=0.61 p=0.5



## Analysis 04.10. Comparison 04 Isocaloric balanced protein supplementation in pregnancy, Outcome 10 Birth head circumference (cm)

Review: Energy and protein intake in pregnancy

Comparison: 04 Isocaloric balanced protein supplementation in pregnancy

Outcome: 10 Birth head circumference (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Mardones 1988 | 391 | 34.16 (1.71) | 391 | 34.32 (1.64) | | 100.0 | -0.16 [ -0.39, 0.07 ] |
| Total (95% CI) | 391 | | 391 | | | 100.0 | -0.16 [ -0.39, 0.07 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.34 p=0.2 | | | | | | | |

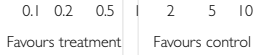

## Analysis 05.01. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 01 Pre-eclampsia

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 01 Pre-eclampsia

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Campbell 1975 | 6/51 | 9/51 | | 60.0 | 0.67 [ 0.26, 1.74 ] |
| Campbell 1983 | 11/91 | 6/91 | | 40.0 | 1.83 [ 0.71, 4.75 ] |
| Total (95% CI) | 142 | 142 | | 100.0 | 1.13 [ 0.59, 2.18 ] |
| Total events: 17 (Treatment), 15 (Control) | | | | | |
| Test for heterogeneity chi-square=2.16 df=1 p=0.14 $I^2$ =53.8% | | | | | |
| Test for overall effect z=0.37 p=0.7 | | | | | |



## Analysis 05.02. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 02 Pregnancy-induced hypertension

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 02 Pregnancy-induced hypertension

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Badrawi 1993 | 15/50 | 17/50 | | 23.6 | 0.88 [ 0.50, 1.57 ] |
| Campbell 1975 | 19/51 | 21/51 | | 29.2 | 0.90 [ 0.56, 1.47 ] |
| Campbell 1983 | 36/91 | 34/91 | | 47.2 | 1.06 [ 0.73, 1.53 ] |
| Total (95% CI) | 192 | 192 | | 100.0 | 0.97 [ 0.75, 1.26 ] |

Total events: 70 (Treatment), 72 (Control)

Test for heterogeneity chi-square=0.40 df=2 p=0.82 $I^2$ =0.0%

Test for overall effect z=0.21 p=0.8


## Analysis 05.03. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 03 Preterm birth

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 03 Preterm birth

| Study | Treatment n/N | Control n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Campbell 1983 | 2/91 | 4/91 | | 100.0 | 0.50 [ 0.09, 2.66 ] |
| Total (95% CI) | 91 | 91 | | 100.0 | 0.50 [ 0.09, 2.66 ] |

Total events: 2 (Treatment), 4 (Control)

Test for heterogeneity: not applicable

Test for overall effect z=0.81 p=0.4

### Analysis 05.04. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 04 Weekly gestational weight gain (g/wk)

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 04 Weekly gestational weight gain (g/wk)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Campbell 1975 | 51 | 228.82 (295.88) | 51 | 575.29 (187.65) | | 50.6 | -346.47 [ -442.63, -250.31 ] |
| Campbell 1983 | 70 | 365.00 (325.00) | 81 | 526.00 (324.00) | | 49.4 | -161.00 [ -264.80, -57.20 ] |
| Total (95% CI) | 121 | | 132 | | | 100.0 | -254.81 [ -436.55, -73.06 ] |

Test for heterogeneity chi-square=6.60 df=1 p=0.01 $I^2$ =84.8%

Test for overall effect z=2.75 p=0.006


### Analysis 05.05. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 05 Birthweight (g)

Review: Energy and protein intake in pregnancy

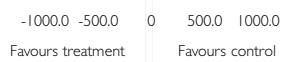
Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 05 Birthweight (g)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Random) 95% CI | Weight (%) | Weighted Mean Difference (Random) 95% CI |
|---|---|---|---|---|---|---|---|
| Badrawi 1993 | 50 | 3500.00 (470.00) | 50 | 3950.00 (420.00) | | 49.1 | -450.00 [ -624.71, -275.29 ] |
| Campbell 1983 | 91 | 3291.00 (473.40) | 91 | 3285.00 (401.60) | | 50.9 | 6.00 [ -121.55, 133.55 ] |
| Total (95% CI) | 141 | | 141 | | | 100.0 | -217.93 [ -664.73, 228.87 ] |

Test for heterogeneity chi-square=17.07 df=1 p=<0.0001 $I^2$ =94.1%

Test for overall effect z=0.96 p=0.3



## Analysis 05.06. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 06 Birth length (cm)

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 06 Birth length (cm)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Campbell 1983 | 83 | 49.82 (2.19) | 85 | 49.84 (1.76) | | 100.0 | -0.02 [ -0.62, 0.58 ] |
| Total (95% CI) | 83 | | 85 | | | 100.0 | -0.02 [ -0.62, 0.58 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=0.07 p=0.9 | | | | | | | |


## Analysis 05.07. Comparison 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain, Outcome 07 Gestational age (week)

Review: Energy and protein intake in pregnancy

Comparison: 05 Energy/protein restriction in pregnant women with high weight-for-height or weight gain

Outcome: 07 Gestational age (week)

| Study | Treatment N | Treatment Mean(SD) | Control N | Control Mean(SD) | Weighted Mean Difference (Fixed) 95% CI | Weight (%) | Weighted Mean Difference (Fixed) 95% CI |
|---|---|---|---|---|---|---|---|
| Campbell 1983 | 91 | 39.56 (1.48) | 81 | 39.31 (1.30) | | 100.0 | 0.25 [ -0.17, 0.67 ] |
| Total (95% CI) | 91 | | 81 | | | 100.0 | 0.25 [ -0.17, 0.67 ] |
| Test for heterogeneity: not applicable | | | | | | | |
| Test for overall effect z=1.18 p=0.2 | | | | | | | |