Review Article

The effect of balanced protein energy supplementation in undernourished pregnant women and child physical growth in low- and middle-income countries: a systematic review and meta-analysis

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Abstract

The beneficial effect of balanced protein energy supplementation during pregnancy on subsequent child growth is unclear and may depend upon the mother entering pregnancy adequately nourished or undernourished. Systematic reviews to-date have included studies from high-, middle- and low-income countries. However, the effect of balanced protein energy supplementation should not be generalised. This review assesses the effect of balanced protein energy supplementation in undernourished pregnant women from low- and middle-income countries on child growth. A systematic review of articles published in English (1970–2015) was conducted via MEDLINE, Scopus, the Cochrane Register and hand searching. Only peer-reviewed experimental studies analysing the effects of balanced protein energy supplementation in undernourished pregnant women from low- and middle-income countries with measures of physical growth as the primary outcome were included. Two reviewers independently assessed full-text articles against inclusion criteria. Validity of eligible studies was ascertained using the Quality Assessment Tool for Quantitative Studies (EPHPP QAT). In total, seven studies met the inclusion criteria. All studies reported on birthweight, five on birth length, three on birth head circumference, and one on longer-term growth. Standardised mean differences were calculated using a random-effects meta-analysis. Balanced protein energy supplementation significantly improved birthweight (seven randomised controlled trials, $n = 2367$; $d = 0.20$, 95% confidence interval, 0.03–0.38, $P = 0.02$). No significant benefit was observed on birth length or birth head circumference. Impact of intervention could not be determined for longer-term physical growth due to limited evidence. Additional research is required in low- and middle-income countries to identify impacts on longer-term infant growth.

Keywords: child growth, international child health nutrition, low-income countries, maternal nutrition, systematic review, underweight.

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Introduction

Rationale

The nutritional status of a woman during pregnancy influences the physical growth of the child. Undernutrition in pregnancy is associated with lowered birthweight, an indicator of intrauterine growth restriction (Stein *et al*. 2004). Low-birthweight babies have a substantially increased risk of stunting by 24 months of age (Martorell *et al*. 1998), leading to irreversible outcomes after 36 months of age, including (1) shorter adult height (Victora *et al*. 2008); (2) lowered immune function and subsequent malnutrition; (3) decreased cognitive function (Pitcher *et al*. 2006); and (4) an

increased risk of chronic disease and maternal complications in later life (Victora *et al*. 2008). Longer-term implications include diminished school achievements and lower adult income (Victora *et al*. 2008).

Little is known about the impact of balanced protein energy supplementation provided throughout pregnancy on birthweight and on the longer-term growth of the child, especially for undernourished women in low- and middle-income countries. A recent Cochrane review (Ota *et al*. 2012) identified that balanced protein energy supplementation during pregnancy significantly improves birthweight and birth length. However, impacts on longer-term growth remain inconclusive as few randomised control trials (RCTs) have reported on this outcome. Ota *et al*.'s review combined adequately nourished and undernourished women, and after stratification, no subgroup differences were identified in terms of birth anthropometrics. A similar review (Imdad & Bhutta 2011) argued that the effect is more pronounced in underweight women with no significant effect in adequately nourished women. Both systematic reviews combined studies from low, middle and higher income countries (Imdad & Bhutta 2011; Ota *et al*. 2012).

Non-RCT studies excluded from both Ota's and Imdad's reviews reported positive findings from maternal supplementation of undernourished women on longer-term growth when the supplement meets an energy gap (Winkvist *et al*. 1998; Tofail *et al*. 2008). Gestational weight gain is strongly associated with fetal growth (Ota *et al*. 2012) and pre-pregnancy weight below 45 kg, or height below 148 cm, are associated with poor fetal outcomes (Kelly *et al*. 1996). In Guatemala, the authors of an RCT, designed to investigate the effect of energy plus protein supplementation vs. energy only, observed a positive impact of energy supplementation on growth when supplementation was provided to mother and child (Lechtig *et al*. 1975). A randomised trial in Bangladesh suggested that supplementation in early pregnancy compared with later pregnancy reduced the proportion of stunting from early infancy up to 54 months for boys, although not for girls (Khan *et al*. 2011). Studies in Bangladesh (Shaheen *et al*. 2006), the Gambia (Ceesay *et al*. 1997) and Taiwan (Adair & Pollitt 1985) report higher birthweight when maternal supplementation coincided with the months immediately after the lean season (Shaheen *et al*. 2006). These findings suggest that balanced protein supplementation is most effective when addressing an energy gap.

The effect of balanced protein energy supplementation during pregnancy on subsequent child growth may depend upon whether the mother enters pregnancy adequately nourished or undernourished; the latter a common circumstance in low- and middle-income countries (Black *et al*. 2013). Thus, it is difficult to generalise the effect of balanced protein energy supplementation from low-, middle- and high-income countries (Imdad & Bhutta 2011). Underweight women in studies from high-income countries are more likely to be suffering from acute malnutrition due to a sudden reduction in food intake, which can result in a lowered weight in both mother and offspring. In contrast, women from studies in low- and middle-income countries are more likely to suffer from chronic malnutrition with bouts of acute malnutrition during times of seasonal food shortages,

Key messages

- First systematic review to-date that analyses the effect of balanced protein energy supplementation during pregnancy in undernourished women of low- and middle-income countries only.
- Between 1970 and 2015, seven unique studies measured the effect of balanced protein supplementation in undernourished pregnant women in low- and middle-income countries on child growth outcomes.
- In low- and middle-income countries, balanced protein energy supplementation has a statistically significant positive impact on the birthweight when the mother is undernourished.
- The impact of balanced protein energy supplementation for undernourished pregnant women on subsequent child growth in low- and middle-income countries remains inconclusive, as the evidence in these studies is not sufficient to determine the effectiveness.

consuming a low energy intake both before and during pregnancy while maintaining usual physical workloads. As reported by Imdad & Bhutta, the effects of balanced protein energy supplementation in undernourished women should not be generalised across low-, middle- and high-income countries. There is a need to review studies from low- and middle-income countries only.

This review identifies the effect of balanced protein energy supplementation during pregnancy on child physical growth in low- and middle-income countries and will identify the significance of targeting specific interventions to different economic contexts. The effect on child growth refers to the effect of balanced protein energy supplementation during pregnancy in undernourished women from low- and middle-income countries and:

1. birthweight,
2. birth length,
3. birth head circumference, and
4. longer-term growth (length/height, weight and head circumference up until 60 months of age).

Materials and methods

Protocol and registration

The PRISMA statement (Moher *et al*. 2011) and the PRISMA Explanation and Elaboration Document (Liberati *et al*. 2009) informed the methodology for this review. The search strategy, methods of analysis and inclusion criteria were specified in advance and documented in a protocol. The review is registered with the international prospective register of systematic reviews (PROSPERO) (Review number: CRD42013005115).

Eligibility criteria

Study

Peer-reviewed articles published in English from 1970 to 2015, describing experimental studies were included in this review – that is, RCTs, controlled before and after studies, and interrupted time-series analyses of routinely collected data. Comparisons

with historical controls or national trends were excluded.

Participants

All studies from low- and middle-income countries involving participants who were identified as undernourished pregnant women. Low- and middle-income country classifications were based on the World Bank 2013 data.[1] This includes studies recruiting undernourished women only, or where within-study stratification was possible between adequately nourished and undernourished women. Undernutrition was not defined, and no common criteria were set. All degrees and definitions specified by each study were of interest, and included. Studies involving participants with groups living with HIV/AIDs and TB were excluded.

Intervention

Eligible studies focused on balanced protein energy supplementation during pregnancy with the outcome being infant and/or child growth. Balanced protein energy refers to macronutrient food-based supplements where the protein provided less than 25% of the total energy content (Kramer & Kakuma 2003). Interventions excluded were those with the primary objective of determining the effects of dietary advice to pregnant women, high protein supplementation (defined as interventions that provided more than 25% of total energy content) and isoenergetic protein supplementation (defined as a supplement where protein replaces an equal quantity of non-protein energy content). Single or multiple micronutrient supplementation studies were excluded unless a balanced protein energy supplement was provided in addition to the multiple micronutrients.

Comparison

Eligible studies had a measurable control so that the impact of the intervention could be assessed. Eligible

[1]The World Bank: Country and Lending Groups (2013). World Bank: Washington, DC. Available from: http://www.data.worldbank.org/country (Accessed 17 July 2013).

controls included 'alternative supplement', 'placebo' and 'no intervention'. Studies that compared a balanced protein energy supplement against a second balanced protein energy supplement were not included.

Outcome

To be eligible for the review, a study must have had published measures of at least one of the following as a primary outcome:

1. Anthropometric measures of the child up to 60 months, including length/height, weight and/or head circumference; and/or
2. Anthropometric measures of intrauterine growth including birthweight, birth length and/or birth head circumference

Information sources

Databases searched were Cochrane, Scopus and MEDLINE via Ovid electronic databases, between 11 March and 28 April 2013. An additional MEDLINE via Ovid search was conducted on 14 January 2015. Reference lists of eligible studies were also manually examined.

Search

The search consisted of four concepts: (i) food based supplementation; (ii) child growth; (iii) malnutrition/deficiencies; and (iv) pregnancy.

Appendix S1 presents a summary of the search strategy for MEDLINE via Ovid. We used the following search strategy and MeSH using MEDLINE via Ovid: *Pregnancy AND *Nutrition Therapy; OR *Food; OR *Micronutrients; OR *Plants, Edible; OR *Nutrition Policy; AND *Nutrition Disorders; OR *Growth Disorders; *Body weight/ or foetal weight; OR *Anthropometry; OR *Nutritional physiological phenomena/ or *child nutritional physiological phenomena/ OR *diet/ or *hunger/ OR *maternal nutritional physiological phenomena/ OR *nutrition processes/ OR *nutritional requirements/ OR *nutritional status/ OR *physiological processes;

AND *Infant. This search strategy was replicated and adjusted as needed for additional searches using Scopus and Cochrane.

Study selection

All identified records were assessed by title or abstract relevancy by one reviewer. Two reviewers independently assessed all selected full text articles for eligibility. Disagreements were resolved through discussion or, if required, through consultation with a third reviewer.

Data collection process

One reviewer extracted data pertaining to the outcomes of interest. Data were entered into spreadsheets and checked by the second reviewer. If data were unclear or not available in the selected paper, additional papers published using data from the same study were reviewed. To avoid duplication, all identified reports were grouped together by its unique study. To resolve inconsistencies, all identified reports under each study were considered.

Data items

We extracted information from each included study on (1) characteristics of the study (year of study implementation, site, design and sample size of intervention and control); (2) characteristics of study participants (age, socio-economic background, nutritional status, inclusion and exclusion criteria); (3) intervention (including type, nutrient composition, amount, duration and frequency); control group (control intervention – type, nutrient composition, amount, duration and frequency; placebo or no intervention); (4) outcome measure [birthweight, birth length, birth head circumference and longer-term growth (weight, height and head circumference)]; and (5) effect on outcome measure [birthweight, birth length, birth head circumference and longer-term growth (weight, height and head circumference)].

Risk of bias in individual studies

The quality of evidence was assessed using the Quality Assessment Tool for Quantitative Studies

developed by the Effective Public Health Practice Project (EPHPP QAT) and guided by the EPHPP reviewers' dictionary (Deeks *et al*. 2003; Thomas *et al*. 2004; Jackson et al. 2005). This tool was validated by Thomas *et al*. (2004) and judged suitable for use in systematic reviews of effectiveness in a review by Deeks *et al*. (2003). The tool calculates an overall methodological rating based on the strength of the study across six sections: (1) selection bias; (2) study design; (3) confounders; (4) blinding; (5) data collection methods; and (6) withdrawals and dropouts. Two sections, (7) intervention integrity and (8) statistical analyses, require consideration however are not included in the overall rating. Sections 1 to 6 received a component rating of 'strong', 'moderate' or 'weak'. A study identified as having two or more weak ratings was identified as weak, one weak rating was moderate and no weak ratings identified the study as strong.

Two reviewers independently completed this process and any discrepancies between the two reviewers with respect to the component ratings were resolved through discussion or, if required, through consultation with a third reviewer.

Summary measures

Random-effects models (Higgins, Green & Cochrane Collaboration 2008; Borenstein *et al*. 2010) were generated for each outcome (birthweight, birth length and birth head circumference). Results are reported as standardised mean differences (Cohen's d) with 95% confidence intervals and *P*-values. Forest plots were created for each outcome. All statistical analyses were carried out using the program Comprehensive Meta Analysis (http://www.Meta-Analysis.com, USA, 2005).

Synthesis of results and risk of bias across studies

We tested for heterogeneity using Q and I^2 statistics. Alpha of 0.05 or less was interpreted as significant. The I^2 test described the percentage of variation across studies that is due to significant heterogeneity rather than random chance. The thresholds outlined in the Cochrane Handbook were used for the interpretation of I^2 (Higgins, Green & Cochrane

Collaboration 2008). To see if heterogeneity varied, sensitivity analyses separated studies identified as weak. For the purpose of the analysis, a Cohen's d score of zero was interpreted as no difference in effect; a result of 0–0.2 was interpreted as a small effect, 0.2–0.5 as a moderate effect and ≥0.8 as a large effect in favour of the intervention.

For cluster RCTs, samples sizes were adjusted in accordance to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins, Green & Cochrane Collaboration 2008). Where no data on outcome-specific intra-cluster correlation coefficients were available, we assumed a value of 0.01 and adjusted the corresponding sample sizes according to the design effect. These methods are similar to those used by Ota *et al*. (2012).

We assessed the possibility of publication bias by evaluating funnel plots as well as calculating classic fail-safe N tests (Higgins, Green & Cochrane Collaboration 2008).

Additional analyses

Additional (subgroup) analyses were conducted to determine whether there were any differences in effect between (1) studies that included some kind of alternative intervention as the control group, and studies where no intervention at all as the control group and (2) studies that supplied micronutrient supplementation in addition to balanced protein energy supplementation as the intervention group, and studies where balanced protein energy supplementation only as the intervention group.

Results

Study selection

Figure 1 (a modified PRISMA flowchart) demonstrates the number of studies and results of the selection and screening process. The search of MEDLINE, Cochrane and Scopus provided 692 citations; 688 after removing duplicates. After screening by title and abstract relevancy, 23 articles were identified for full-text review. An additional 16 articles were identified
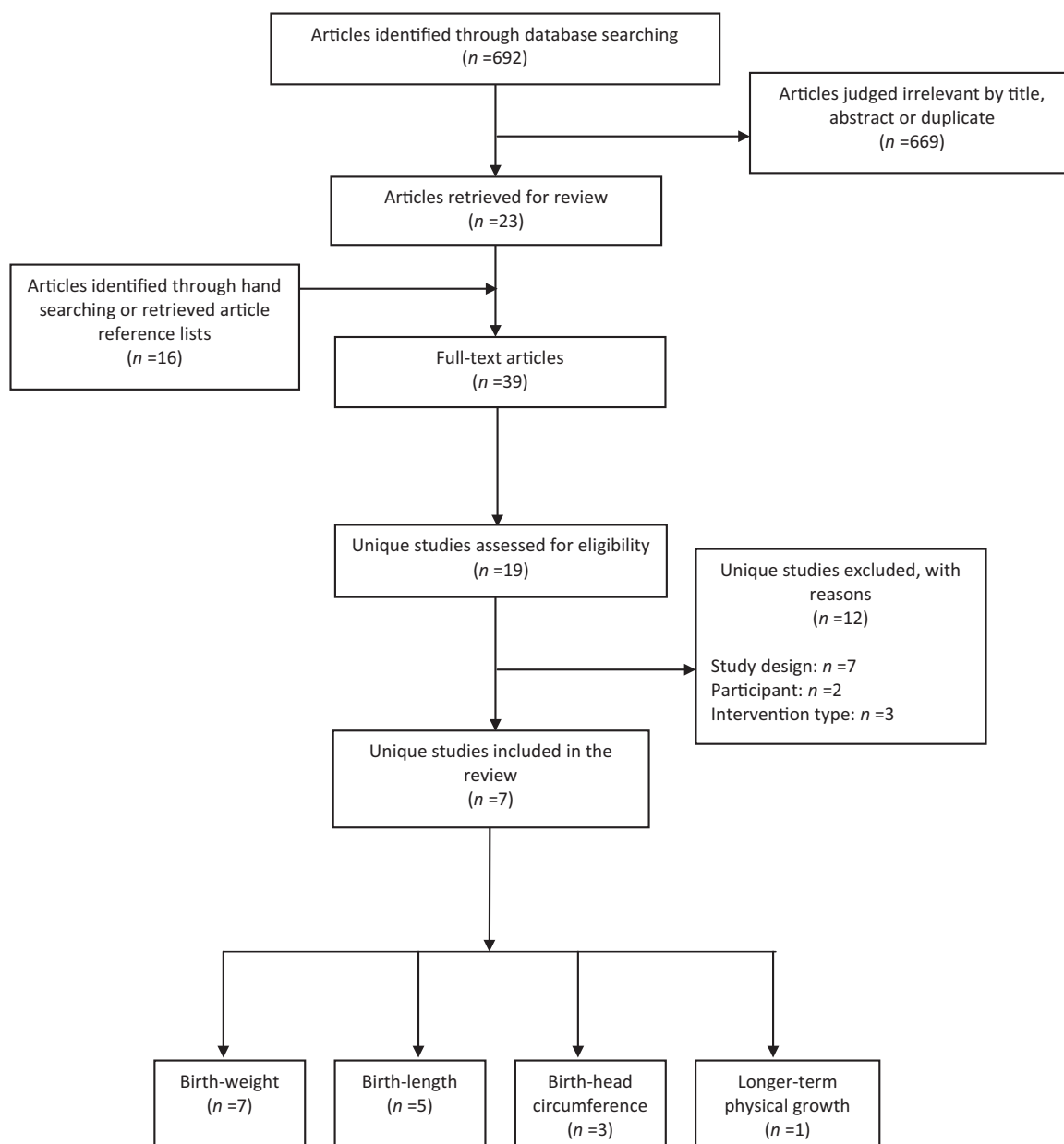
Fig. 1. Summary of search for selected articles (modified from PRISMA flowchart).

through manually searching the reference lists of retrieved articles, yielding a total of 39 articles. The 39 articles were categorised by unique study, and in total, 19 unique studies were identified. After reading the full text of these studies, 12 studies were excluded based on inclusion criteria (study design: 7; intervention type: 3; participants: 2). Therefore, a total of seven

unique studies were included in the review. Table S1 presents the characteristics of the excluded studies.

Study characteristics

The seven studies included in the review are summarised in Table 1 (Mora *et al.* 1979; McDonald *et al.*

Table 1. Characteristics of included studies

Allocated code	Study details	Subjects	Study group intervention	Control group	Intake	Outcomes relevant to systematic review
McDonald (a)	Year study initiated 1967 Site Taiwan Study design RCT Sample size intervention 114 Sample size control 111	Selected based on low socio-economic rank, between ages 19 and 30 from 14 farming villages. Have at least one 'healthy' male child, in second or third trimester of pregnancy. Planning on having at least one more child.	Chocolate flavoured energy and nutrient-rich liquid supplement. Plus micronutrient supplement.	Received placebo beverage. First 4 years, 6 kcal day^{-1} and then 40 kcal day^{-1} as artificial sweetener replaced with sucrose. Micronutrients added in the last year near completion of study.	Two servings per day. Start: 3 weeks prior to birth of first child. End: after 15 months of lactation for the second. Issues No baseline data. 24-h dietary recall did not include snacks. Control supplementation changed after 4 years.	Mean birthweight, gender sensitivity, birth length, infant weight, length and head circumference
	Findings No significant impact on low birthweight. Evidence of a threshold for the impact of caloric intake on birthweight where there is calorie gap. Effect of supplement greater during the hungry season, on birthweight of relatively thin mothers compared with control. Birthweight of the second male child was statistically higher than that of the first infant in the high supplement group. No effect on longer-term physical growth.					
Ceesay (b)	Year study initiated 1989 Site Gambia Study design Cluster RCT Sample size intervention 1460 Sample size control 1037	Chronically undernourished women from 28 villages	Groundnut biscuit (groundnut, rice flour, sugar, groundnut oil). Feeding centre – direct observation daily by two birth attendants.	Received supplement after pregnancy	Two biscuits, 6 days a week. Start: 20 weeks pre-delivery. Issues Data available until 36 months of infancy; however, the control received intervention post-delivery and lactating mothers were supplemented	Birthweight, birth length, head circumference
	Findings Supplement increased birthweight and head circumference in lean season only. Positive effects likely to be seen where women are malnourished.					
Girija (c)	Year study initiated 1984 Site India Study design RCT Sample size intervention 10 Sample size control 10	Lower socio-economic women aged 20–33	50 g of sesame cake, 40 g of jaggery and 10 g of oil	No supplement	Servings and distribution not described. Start: second and third trimester. Issues No information on compliance or dietary substitution. Energy and protein intake higher prior to supplementation in both groups. No SDs reported on post-natal anthropometric outcomes. Inadequate description of allocation.	Birthweight, birth length, head circumference
	Findings No significant impact on birthweight or length could be due to small sample size. Multiple correlation and multiple regression analyses showed that birthweight of the infant was positively associated with protein and energy intake.					
Huybregts (d)	Year study initiated 2009 Site Burkina Faso Study design RCT Sample size intervention 641 Sample size control 655	Women of reproductive age	Lipid nutrient spread (LNS) comprise of 33% peanut butter, 32% soy flour, 15% vegetable oil and 20% sugar. Plus daily multiple micronutrient supplementation (UNIMMAP) meeting pregnancy recommended nutrient intake (RNI).	Multiple micronutrient tablet	1 serving daily. Produced by local women's association. Start: first or second trimester.	Birthweight, birth length, longer-term anthropometrics (weight and height)
	Findings Significant impact on birth length 0.5 cm ($P = 0.001$), hypothesised to be linked to the high fat content. Direct link unknown. Impact on weight though not significant.				Issues Control received multiple micronutrients, which are known to increase birthweight, reducing gap between control and intervention	

Table 1. Continued

Allocated code	Study details		Subjects	Study group intervention	Control group	Intake	Outcomes relevant to systematic review
Kardjati (e)	Year study initiated	1992	Nutritionally vulnerable women at 26–28 weeks of gestation	Protein energy drinks (sunflower, palm oil in text aid added to hot beverage) with casein and glucose	Control supplement of low protein energy drink 52 kcal and 6.2 protein	200 mL per serving. One package each day observed by fieldworker that delivered to house.	Birthweight, ongoing growth of child to 60 months
	Site	Indonesia					
	Study design	RCT					
	Sample size intervention	276					
	Sample size control	266					
	Findings						
	No impact on birthweight, although an increase in birthweight of the total sample (intervention and control) compared with baseline period. Supplementation proved beneficial if meeting an energy gap. Intervention children were significantly heavier than control children ($P < 0.05$). Intervention children were also taller throughout the first 5 years ($P < 0.05$ from 15 to 48 months, $P = < 0.05$ at both 3–12 and 60 months). Wasting was similar in both groups, although stunting was less prevalent in intervention children.					Issues	
						Data suggest much higher calorie and protein intake in control than anticipated. Only children of mothers who had complied for at least 90 days were included in longer-term follow-up (attrition bias).	
Mora (f)	Year study initiated	1975	Lower socio-economic women. Women recruited in first/second trimester and received supplement in third trimester of pregnancy. >50% of children in household malnourished.	Weekly food basket for whole household (milk powder, bread and vegetable oil). Pregnant women instructed to consume usual diet and to treat supplementation as 'additional' food.	No supplement. Received measurements and health care	Food basket to be shared with whole household. Iron and vitamin A as a micronutrient tablet/capsule.	Birthweight
	Site	Colombia					
	Study design	RCT					
	Sample size intervention	207					
	Sample size control	200					
	Findings						
	Significant correlation between maternal supplementation and weight gain during pregnancy in women giving birth to male offspring. Also significant impact on the mean birthweight of males although not females compared with control.					Issues	
						Reported that women only got 9% of intended kcal intake; 150 of 850 women recruited in first/second trimester and received supplement. Supplement given to child at 3 months, therefore data on child growth not used in this review.	
Tontisirin (g)	Year study initiated	1986	Non-smoking pregnant women age 16–30 from rural areas and of same socio-economic status. Selected from women who attended maternal health centres. First or second trimester. All in good health with low caloric intake.	Locally available supplementary food. Two formulas tested in two of the experimental groups; 1 group representation four potential formulas and the other a fifth formula. Each group provided similar caloric value.	No supplementation	Supplement provided as single serving packets, and consumed as a snack	Birthweight, birth length and birth head circumference
	Site	Thailand					
	Study design	RCT					
	Sample size intervention	28					
	Sample size control	15					
	Findings						
	Significant impact on birthweight in both supplemented groups, although no significant impact on length or head circumference					Issues	
						Number of women originally allocated not stated. Many statistical errors throughout report. Reported, as an RCT though would have been more suited as an acceptability study.	

RCT, randomised controlled trial.

1981; Girija *et al.* 1984; Tontisirin *et al.* 1986; Kardjati *et al.* 1988; Ceesay *et al.* 1997; Huybregts *et al.* 2009). More than one article was published describing the findings of three of these seven studies. Articles were categorised by the unique study's first published article lead author, as follows: Huybregts *et al.* (2009) (Lanou *et al.* 2014); Kardjati *et al.* (1988) (Kardjati *et al.* 1990; Kusin *et al.* 1992); and McDonald *et al.* (1981) (Wohlleb *et al.* 1983; Mueller & Pollitt 1984; Adair & Pollitt 1985). The studies are coded as follows (a) McDonald, (b) Ceesay, (c) Girija, (d) Huybregts, (e) Kardjati, (f) Mora, and (g) Tontisirin. Of the seven studies included in the review, six were RCTs (a, c, d, e, f, g) and one a cluster RCT (b). All studies were from low- and middle-income countries with the primary outcome to measure the difference in physical growth (weight, height, head circumference) between intervention and control groups of the child. The main inclusion criteria entailed pregnant women in second or third trimester from lower socio-economic groups. Included studies involved 2367 participants. In five of the studies (b, c, e, f, g), all women were identified as undernourished. Two of the five studies (a, d) included adequately nourished and undernourished women; however, within-study stratification was possible and data from nourished women were excluded.

Of the seven studies, one study (d) adjusted for gestational age, health centre- based recruitment and malaria prevention initiatives; one study (b) adjusted for sex, primiparity, Parkin score, gestational age, maternal parity, sex of the baby, and seasonality; three studies (a, e, f) conducted intergroup analyses on identified variables that may confound the main treatment–outcome relationship although did not adjust as no significant relationship were identified; and two studies (c, g) did not report on potential confounding variables.

The degree of undernutrition and its definition varied across studies. Two studies included all eligible participants without using an indicator to determine nutritional status, and the results were then stratified by adequately nourished and undernourished without providing the cut-off used to define undernourished (a, d). One study defined women as chronically malnourished or food insecure; however, the indicator used to define 'chronically malnourished' was not published (b). Three studies identified women as malnourished without a measure or definition provided (c, f, g). One study that identified women as nutritionally vulnerable failed to define undernutrition and did not use an anthropometric indicator (e).

Data from two studies included for the assessment of intrauterine growth were excluded for the assessment of child growth as one study supplemented the child from 3 months of age (f), and one study did not provide a measure of variation such as a standard deviation (c).

The seven interventions received are summarised in Table 2. The type of intervention received included a chocolate flavoured energy drink (a), groundnut biscuits (b), varying food baskets containing local produce (c, f, g), a lipid nutrient spread (d) and a protein energy drink (e). Selected studies had a diverse range of controls. Three studies were supplementation vs. control supplementation (a, d, e), one study provided the supplement to the control group on delivery of child (b), and three studies were supplementation vs. no intervention (c, f, g). Of the control supplements, two (a, e) were similar to the intervention in taste, colour and texture, with low amounts of energy, and the third was a multiple micronutrient supplement (d).

Risk of bias in individual studies

Figure 2 illustrates the quality of evidence using EPHPP ratings. Of the seven included studies, two were identified as strong (d, e), three studies (a, b, f) as moderate and two as weak (c, g). Two studies were not likely to be representative (c, g), two studies (c, g) did not report on the number of participants that agreed to participate in the study and two studies (a, c) did not report on methods of randomisation. The anthropometric staff were blinded in two studies (a, d) to reduce measurement bias, while the outcome assessor/s were aware of the exposure in two studies (b, e) and it was not possible to identify whether they were aware of exposure or not for three studies (c, f, g). Two studies (c, g) did not report withdrawals and dropouts in terms of numbers and/or reason per group and one study did not indicate the percentage of participants completing the study (g) (see Table 3 for further details).

Table 2. Nutrient composition of balanced protein energy supplementation

	Nutrients provided by supplement per day*						Tontisirin One serve		RNI† for pregnant women
	MacDonald Two cans	Ceesay Two biscuits	Girija One serve	Huybregts One serve	Kardjati One serve	Mora Average from weekly food basket	Formula 1	Formula 2	
Energy‡ (kJ)	3347	4247	1745	1559	1946	3582	1607	1456	9519§
Protein (g)	40	22	30	14.7	7.1	38.4	15	13.1	71¶
% Energy from protein**	20.0	8.7	<25††	15.8	6.1	17.9	15.6	15.1	10–35%‡‡
Fats§§ (g)	26.6	56		27.6	25.8		9.1	15.6	ND¶¶
% Energy from fat***	29.9	49.7		66.7	49.9		21.3	40.3	20–35%
Carbohydrates (g)	100			15.9	46.5	0.0			175†††
Vitamin A (µg RE)	5000			2936		6024			800‡‡‡
Cholecalciferol (µg)	10			5					5
Vitamin E (mg TE)				13					7.5§§§
Thiamine (mg)	1.6			1.6					1.4
Riboflavin (mg)	1.8			1.6					1.4
Niacin (mg)	20			21					18
Vitamin B6 (mg)	1.6			2					1.9
Folic acid (µg DFE¶¶¶)	0			461					600
Vitamin B12 (µg)	2			2.6					2.6
Pantothenic acid (mg)	7.36								6
Ascorbic acid (mg)	75			71					55
Calcium (mg)	1000	47		90			86.4	165.6	1200
Iron (mg)	12	1.8		35		18	7.02	3.9	NA****
Zinc†††† (mg)	0			17					10
Iodine (µg)	0			150					200
Selenium (µg)				65					30

TE, Tocopherol equivalents. *Blank cell indicates no available information. †Recommended Nutrient Intake (RNI) values as identified by WHO/FAO, 2004 (World Health Organization. & Food and Agriculture Organization of the United Nations. 2004). RNI is the daily intake that meets the nutrient requirements of almost all (97.5%) apparently healthy individuals in an age- and sex-specific population. RNI, as used above, is equivalent to that of the recommended dietary allowance (RDA) as used by the Food and Nutrition Board of the United States National Academy of Sciences. ‡1 kcal = 4.184 kJ. §Energy requirements based on a developing country profile (demography and anthropology) as defined by WHO, et al, 2004 (WHO et al. 2004). ¶Recommended Dietary Allowance sourced from the Food and Nutrition Board (U.S) (Institute of Medicine (U.S.). Panel on Macronutrients. & Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. 2005). RDA is the average daily dietary intake level; sufficient to meet the nutrient requirements of nearly all (97–98%) health individuals in a group. **Calculated by {total grams of protein/(total energy from protein)/(total energy in supplement) × 100} as recommended by WHO, et al. 2004 (WHO et al. 2004). ††Reported as a balanced protein energy supplement by Ota et al. (2012). Ota et al. had access to unpublished data. ‡‡Threshold as stated by WHO, et al, 2004 (WHO et al. 2004). §§Did not include linoleic or alpha-linolenic acid as no included study reported on this. ¶¶Calculated by [total g of fat × 9] {(total energy from fat)/(total energy in supplement) × 100} as recommended by WHO, et al, 2004 (WHO et al. 2004). ***Based on energy from fat. ¶¶¶Calculated by [total g of fat × 9] {(total energy from fat)/(total energy in supplement) × 100} as recommended by WHO, et al, 2004 (WHO et al. 2004). †††RDA sourced from the Food and Nutrition Board (U.S) (Institute of Medicine (U.S.). Panel on Macronutrients. & Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. 2005). ‡‡‡RDA sourced from the Food and Nutrition Board (U.S) (Institute of Medicine (U.S.). Panel on Macronutrients. & Institute of Medicine (U.S.). Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. 2005). §§§No current evidence to suggest that vitamin E requirements during pregnancy differ from those of other adults. ¶¶¶Dietary folate equivalents: micrograms of DFE provided = [micrograms of food folate + (1.7 × micrograms of synthetic folic acid)]|[(total grams of fat from fat)/(total energy in supplement) × 100]. ****WHO/FAO recommends that iron supplements in tablet form be given to all pregnant women because of the difficulties in correctly assessing iron status in pregnancy. ††††Based on moderate availability.

	Selection Bias	Study Design	Confounders	Blinding	Data collection methods	Withdrawals and Drop outs	**Global Rating**
Quality of Evidence - STRONG
[d]Huybregts, 2009	STRONG	STRONG	STRONG	MODERATE	STRONG	STRONG	STRONG
[e]Kardjati, 1988	STRONG	STRONG	STRONG	MODERATE	STRONG	MODERATE	STRONG
Quality of Evidence - Moderate
[a]McDonald, 1981	STRONG	MODERATE	MODERATE	WEAK	STRONG	MODERATE	MODERATE
[b]Ceesay, 1989	STRONG	STRONG	MODERATE	WEAK	STRONG	MODERATE	MODERATE
[f]Mora, 1975	STRONG	STRONG	STRONG	WEAK	STRONG	STRONG	MODERATE
Quality of Evidence - WEAK
[c]Girija, 1984	WEAK	WEAK	MODERATE	WEAK	STRONG	MODERATE	WEAK
[g]Tontisirin, 1986	WEAK	MODERATE	MODERATE	WEAK	MODERATE	WEAK	WEAK

STRONG	(green)
MODERATE	(orange)
WEAK	(red)

Fig. 2. EPHPP global ratings.

Risk of bias across studies

The classic fail-safe N test indicated that 27 additional negative studies were required to change the significance of the effect of supplementation on birthweight. The fail-safe test was not applicable to other findings (Higgins, Green & Cochrane Collaboration 2008). Funnel plots were considered as an unreliable source of judgement as there were only seven studies included in this review, which is below the recommended level of 10 studies for funnel plot analyses (Higgins, Green & Cochrane Collaboration 2008).

Results of individual studies/syntheses of results

Evidence of moderate to high heterogeneity between the seven included studies was observed, as indicated by the Q and I^2 values. This was also true for the stratified analyses on each of the outcome measures. The random effects models were used to estimate standardised mean difference as it was the most appropriate model due to the heterogeneity of the included studies (Borenstein *et al*. 2010).

Data on birthweight from undernourished mothers were available from all seven studies (intervention: $n = 1228$; control: $n = 1139$). While an increase in birthweight was observed in the intervention group for six of the seven studies (a, b, c, d, f, g), this was statistically significant in three studies only (b, f, g). For two of the seven studies, data were stratified by undernourished and adequately nourished (a, d). Data on adequately nourished were excluded, and only data on undernourished were included in the analysis. For one study (g), the intervention group received one of two potential supplements, but only one group (group 1) was used for the analysis. The pooled results from these studies indicate that supplementation had a significant moderate effect on birthweight [RCT = 7, intervention: $n = 1228$; control: $n = 1139$; d = 0.20, 95% confidence interval (CI): 0.03–0.38, $P = 0.02$]. No significant findings were identified

Table 3. Quality of evidence findings

Number of studies	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Intervention integrity	Analysis
Quality of evidence – STRONG								
2 [d, e]	Two studies recruited participants that are very likely to be representative of the target population. Number of individuals that agreed to participate reported for each study.	Two studies reported as RCTs and as described as randomised. Methods of randomisation explained for each study and identified in review as appropriate.	Two studies reported no important differences between groups prior to the intervention.	The anthropometric outcome assessor(s) were not aware of the intervention/exposure status of participants in one study (d). Could not identify whether participants were aware of the research question in two studies.	Data collection methods were identified as valid and reliable in two studies	Two studies reported on withdrawals and dropouts in terms of numbers and/or reasons per group. Two studies indicated the percentage of participants completing the study.	Two studies reported the number of participants received the allocated intervention. Unlikely that the subjects received an unintended intervention that may influence the results in two studies.	Unit of allocation at individual level for two studies. Analysis conducted at individual level for two studies.
Quality of evidence – MODERATE								
3 [a, b, f]	Three studies recruited participants that are very likely to be representative of the target population. Three studies reported the number of individuals that agreed to participate.	Two studies reported as RCTs (a, f) and one study as a cluster RCT (b). All studies described as randomised, methods of randomisation not reported for one study (a), and identified as appropriate for two studies (b, f).	Three studies reported no important differences between groups prior to the intervention.	The outcome assessor(s) were aware of the intervention or exposure status of participants for one study (b), not aware for one study (a), and was not reported for one study (f). Could not identify whether participants were aware of the research question in three studies.	Data collection methods identified as valid and reliable in three studies	Three studies reported on withdrawals and dropouts in terms of numbers and/or reasons per group. Three studies indicated the percentage of participants completing the study (a, b, f).	Three studies reported the number of participants that received the allocate intervention. Likely that participants received an unintended intervention that may influence results in one study (a).	Unit of allocation and analysis at individual level for two studies (a, f), and at community level for one study (b). Statistical methods identified as appropriate for three studies.
Quality of evidence – WEAK								
2 [c, g]	Two studies recruited participants that are not likely to be representative of the target population. Could not identify the percentage of selected individuals that agreed to participate in two studies.	Two studies reported as RCTs and as randomised. Methods not reported in one study (c), and not identified as appropriate (g).	Could not identify important differences between groups for one paper (c), and not reported in one paper (g)	Could not tell if the outcome assessor(s) were aware of the intervention or exposure status of participants for two studies and could not identify whether participants were aware of the research question for two studies	Data collection methods identified as valid and reliable in two studies	Two studies did not report on withdrawals and dropouts. One study indicated the percentage of participants completing the study (c) and could not identify for one study (g).	One study reported the number of participants that received the allocated intervention (c), and could not tell for one study (g). Unlikely that subjects received an unintended intervention that may influence results in two studies.	Unit of allocation and analysis at individual level for two studies. Statistical methods identified as appropriate for two studies.

RCTs, randomised controlled trials.

in the subgroup analyses of intervention vs. alternative intervention control group (a, b, d, e) (RCT = 4; intervention: n = 997; control: n = 914; d = 0.17, 95% CI: –0.06–0.40; P = 0.15), and subgroup analyses of intervention vs. no intervention control group (c, f, g) (RCT = 3; intervention: n = 231; control: n = 225; d = 0.41, 95% CI: –0.08–0.90, P = 0.10). However, a small and moderate impact in favour of the intervention was observed, respectively. In one of these studies (c), a higher percentage of energy from protein (>25%) was included in the intervention supplement even though the authors identified the supplement as balanced. When this study was excluded from the pooled analysis, the effect of supplementation was slightly reduced but remained significant (RCT = 6, intervention: n = 1218; control: n = 1129; d = 0.19, 95% CI: 0.01–0.37, P = 0.04). Two of the included studies also included micronutrient supplements in addition to balanced protein energy supplements as part of the intervention (a, d). When these studies were excluded from the pooled analysis, the effect of supplementation was reduced (RCT = 5; intervention: n = 1109; control: n = 1030; d = 0.18, 95% CI –0.04–0.39; P = 0.11). However, in one of these studies (d), the control group was given the micronutrient supplementation (and the intervention group was given balanced protein energy as well as micronutrient supplementation), so the observed effect size can be attributed to the balanced protein energy supplementation. When this study is included in the pooled results, a similar effect size is yielded,

and approaches significance (intervention: n = 1173; control: n = 1084; d = 0.18; 95% CI: –0.01–0.37; P = 0.06). See Figure 3 for further details.

Data on birth length were available from five studies (a, b, c, d, g) (intervention: n = 683; control: 615). Of the five studies measuring the impact of supplementation on birth length, one study reported a statistically significant impact on birth length (d), two studies reported no significant impact although did identify an increase in length (c, a) and two studies reported no effect at all (b, g). For the meta-analyses, the data from two studies were stratified by undernourished and adequately nourished (a, d). Data on adequately nourished were excluded, and only data on undernourished were included in the analysis. For one study (g), only group 1 from the two supplemented groups was used for the analysis. The pooled results from these studies indicate that supplementation had a small effect in favour of the intervention, albeit not significant (RCT = 5, intervention: n = 683; control n = 615; d = 0.22; 95% CI: –0.04–0.50; P = 0.10). No significant findings were identified in the subgroup analyses of intervention vs. alternative intervention control group (RCT = 3, intervention: n = 659; control n = 590; d = 0.196; 95% CI: –0.10–0.49; P = 0.18) and subgroup analyses of intervention vs. no intervention control group (RCT = 2, intervention: n = 24, control: n = 25; d = 0.40; 95% CI: –0.47–1.27; P = 0.37). However, a small and moderate impact in favour of the intervention was observed, respectively. When the study (g) that included >25% of energy from protein was
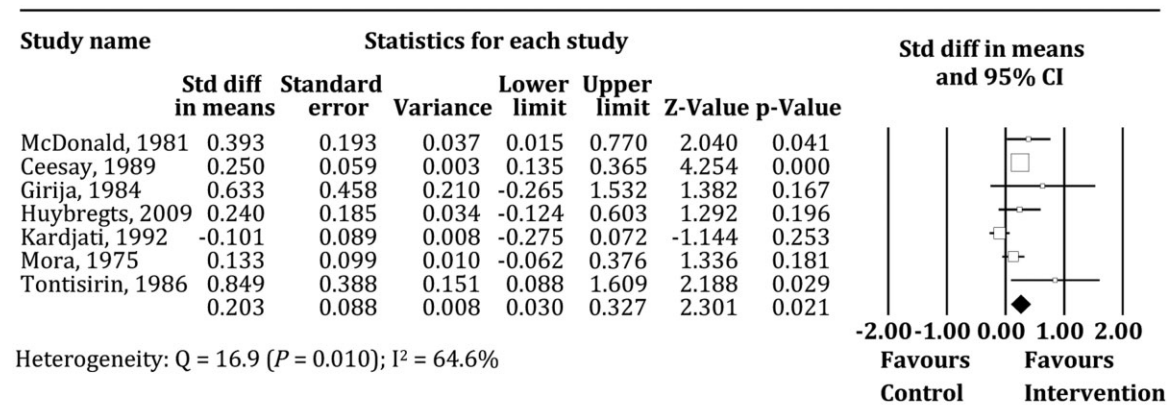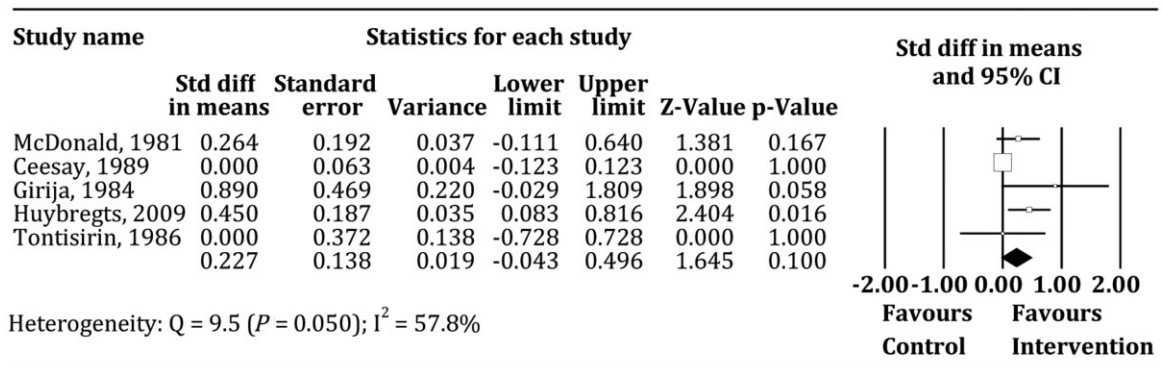
Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Std diff in means and 95% CI
McDonald, 1981	0.393	0.193	0.037	0.015	0.770	2.040	0.041	
Ceesay, 1989	0.250	0.059	0.003	0.135	0.365	4.254	0.000	
Girija, 1984	0.633	0.458	0.210	-0.265	1.532	1.382	0.167	
Huybregts, 2009	0.240	0.185	0.034	-0.124	0.603	1.292	0.196	
Kardjati, 1992	-0.101	0.089	0.008	-0.275	0.072	-1.144	0.253	
Mora, 1975	0.133	0.099	0.010	-0.062	0.376	1.336	0.181	
Tontisirin, 1986	0.849	0.388	0.151	0.088	1.609	2.188	0.029	
	0.203	0.088	0.008	0.030	0.327	2.301	0.021	

Heterogeneity: Q = 16.9 (P = 0.010); I^2 = 64.6%

-2.00 -1.00 0.00 1.00 2.00
Favours Control   Favours Intervention

Fig. 3. Effect of balanced protein energy supplementation on birthweight (n = 7).

Fig. 4. Effect of balanced protein energy supplementation on birth length (*n* = 5).

excluded from the pooled analysis, the effect of the supplementation was reduced (RCT = 4, intervention: *n* = 673; control: *n* = 605; d = 0.17, 95% CI: −0.08–0.41, *P* = 0.18). When the two studies that also included micronutrient supplements in addition to balanced protein energy supplements as part of the intervention (a, d) were excluded from the pooled analysis, the effect of supplementation was reduced (RCT = 3; intervention: *n* = 564; control: *n* = 506; d = 0.14; 95% CI −0.27–0.55; *P* = 0.51). However, when the study (d) for which the control group was given the micronutrient supplementation (and the intervention group was given balanced protein energy as well as micronutrient supplementation) was included in the pooled results, the effect size increased but was still not significant (intervention: *n* = 628; control: *n* = 560; d = 0.24; 95% CI: −0.12–0.19; *P* = 0.19). See Figure 4 for further details.

Data on birth head circumference were available from three studies (b, c, g) (intervention: *n* = 553; control: *n* = 499). Stratification for two studies by undernourished and adequately nourished women was not possible (a, d) and therefore excluded from the analyses. Of the three studies measuring the impact of supplementation on head circumference, one study identified a statistically significant increase during the lean season only (b), one study identified a slight increase in intervention group, although not significant (g) and one study identified no effect (c). For one study (g), only group 1 was used for analysis. The pooled results from these studies indicate that supplementation had a small effect on birth head circumference in favour of the intervention, but this was not significant

(RCT = 3, intervention: *n* = 553; control: *n* = 499; d = 0.17; 95% CI: −0.07–0.41; *P* = 0.17). This did not change when the study (g) with >25% of energy from protein was excluded from the analyses. Subgroup analyses of intervention vs. alternative intervention control group were not possible due to number of studies in analyse (*n* = 1). Subgroup analyses of intervention vs. no intervention control group identified a moderate impact in favour of the intervention, albeit not significant (RCT = 2, intervention: *n* = 20; control: *n* = 24; d = 0.26; 95% CI: −0.62–1.14; *P* = 0. 56). See Figure 5 for further details.

Effect on longer-term growth

Only one study showed the impact of supplementation on the longer-term growth of a child (e). This study showed a significant difference for height until 60 months and weight until 24 months of age with a greater effect at 9 and 12 months, respectively. One additional study that measured impact of supplementation on longer-term growth however was excluded from analyses, as within-study stratification of infants born of mothers nourished or undernourished during pregnancy was not possible (a).

Discussion

Summary of evidence

The seven studies in this review included six (a, c, d, e, f, g) RCTs and one cluster RCT (b). We included one study (Tontisirin *et al.* 1986) not included in Ota
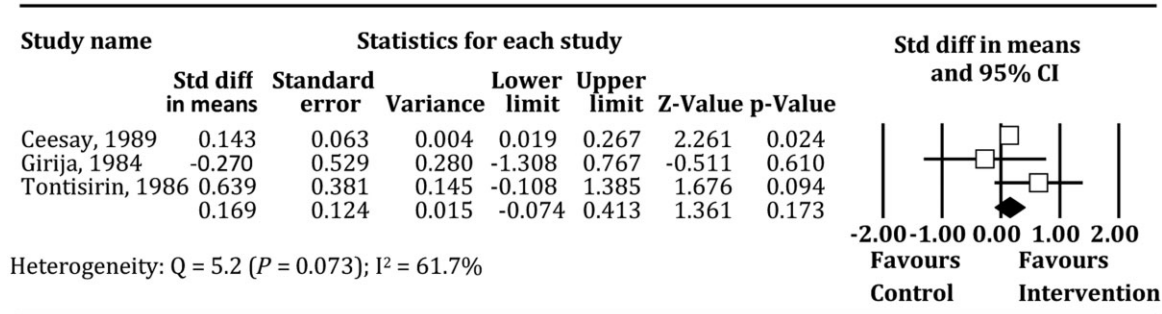
Fig. 5. Effect of balanced protein energy supplementation on birth head circumference ($n = 3$).

et al.'s (2012) review and three (Tontisirin *et al*. 1986; Kardjati *et al*. 1990; Huybregts *et al*. 2009) studies not included in the review of Imdad & Bhutta (2011). This review excluded all studies from high-income countries, which were included in the reviews of Ota *et al*. and Imdad & Bhutta.

Evidence from studies reporting on the impact of supplementation of undernourished pregnant women on fetal outcomes suggested a statistically significant positive effect on birthweight. As the interventions varied, the use of different controls is understandable; however, this creates some difficulties when pooling data and generalising the results across studies. Subgroup analyses identified that when no control supplement was used, the effect between the intervention and control increased from small to medium, indicating that supplementation has a greater impact when there is a larger energy gap to meet. This finding is supported by other studies (McDonald *et al*. 1981; Winkvist *et al*. 1998; Tofail *et al*. 2008).

We identified discrepancies in one study (Girija *et al*. 1984), between the manual calculations and published data (Imdad & Bhutta 2011; Ota *et al*. 2012), for the percentage of energy from protein for the intervention supplement. As reported in the Results section, when Girija's study was excluded from the pooled analyses, the effect sizes of the intervention were reduced for birthweight and birth length, and remained the same for birth head circumference. The changes in effect size were small, and this is likely because there were only 20 participants in the Girija study. This finding suggests that when compared to balanced protein energy supplements, a protein energy supplement with a higher percentage of

energy from protein may have a positive effect on birthweight. Recent evidence from a Cochrane review contradicts this (Ota *et al*. 2012). In their review, Ota *et al*. identified that high-protein supplementation was associated with a significantly increased risk of small-for-gestational age babies. The energy from protein in the Girija study was 28.8%, and the energy from protein in the review by Ota and colleagues was 34.0% (Rush *et al*. 1980). Hence, the conflicting findings may suggest that protein energy supplementation is most effective when the percentage of energy from protein meets a certain threshold.

The impact of balanced protein energy supplementation for undernourished pregnant women on subsequent child growth in low- and middle-income countries remains inconclusive, as the evidence from one study is not sufficient to determine the effectiveness. This finding supports the results of Kramer and Kakuma's Cochrane review conducted in 2003 (Kramer & Kakuma 2003), which identified that there were an insufficient number of studies to draw a conclusion on the impact of balanced protein energy supplementation on longer-term child growth. Only one study reviewed reported on longer-term child growth outcomes, until 60 months of age. This study identified a significant increase in height and weight of the child, until 60 and 24 months, respectively. However, this study excluded poor compliers; thus, definitive conclusions cannot be made.

Limitations

The main limitations of this review are that the participant population, the form of supplement, the control

intervention and the outcome definitions are not consistent across studies. In addition, the definition of malnutrition varied across studies, and the differential effects of supplementation at these different levels are difficult to generalise. The quality of the studies varied, including the methods of randomisation, blinding of anthropometric staff, and reporting on withdrawals and dropouts. One study provided multiple micronutrient supplementation to the control (d), which is known to increase birthweight (Lumey *et al.* 1995), thus reducing a potential gap; one study provided the intervention to the woman pre-and post-pregnancy (a), making it difficult to identify the effect of supplementation during pregnancy only; four studies did not blind the anthropometric data collectors (c, e, f, g); three studies did not report on compliance (c, f, g); one study excluded poor compliers from analyses on longer-term growth and thus did not adhere to the intention-to-treat principle (e); and two studies provided a multiple micronutrient supplementation to the control (a, d).

Discrepancies across studies may have affected the findings. It is difficult to ascertain the direction of the impact of the sources of bias in the included studies on the results of these studies (and the meta-analyses completed for this review). For example, lack of blinding of anthropometric staff and excluding poor compliers from analyses may have improved the effect of the intervention. Conversely, poor compliance may reduce the effect of the intervention.

Low- and middle-income countries were classified using the 2013 World Bank data. While countries that transitioned from middle to high income from 1970 to 2013 were excluded, when conducting the systematic review, no studies from transitioned middle- to high-income countries were identified. Due to resource limitations, the studies were limited to English-language publications only. While studies were limited to English-language publications only, manually searching the reference lists of retrieved articles identified no additional publications in other languages.

Conclusion

Between 1970 and 2015, seven studies measured the effect of balanced protein supplementation of under-nourished pregnant women in low- and middle-income countries on child growth outcomes. This review identifies that in low- and middle-income countries, balanced protein energy supplementation has a positive impact on the birthweight when the mother is undernourished. Scaling up this intervention would improve the nutritional status of otherwise nutritionally vulnerable children; however, additional research is required on the cost-effectiveness of the interventions compared with others. The effect of supplementation on longer-term physical growth remains inconclusive due to the small number of well-designed studies that have measured this outcome. The findings of this review support those reported in an earlier review (Ota *et al.* 2012). The opportunity exists to invest in new robust studies to identify whether protein energy supplementation targeting undernourished pregnant women affects the longer-term growth of a child in low- and middle-income countries.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

BS, PB and JJ co-developed the research question. BS conducted the search. BS and JJ assessed all selected full text articles for eligibility. BS and JJ assessed the quality of evidence for selected full text articles. BS and PB conducted the meta-analyses. PB, KW and BS analysed and interpreted the data. BS wrote the first draft of the paper, which was revised with editorial input from JB, PB, KW, AC, JJ, and blind reviewers at

the Journal of Maternal and Child Nutrition. BS developed the figures and tables.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Characteristics of excluded studies.
Appendix S1. Summary of search strategy for Medline via Ovid.
Appendix S2. PRISMA 2009 checklist.