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Maternal Nutrition and Birth Outcomes: Effect of Balanced Protein-Energy Supplementation

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Abstract

The nutritional status of a woman before and during pregnancy is important for a healthy pregnancy outcome. Maternal malnutrition is a key contributor to poor fetal growth, low birthweight (LBW) and short- and long-term infant morbidity and mortality. This review summarised the evidence on association of maternal nutrition with birth outcomes along with review of effects of balanced protein-energy supplementation during pregnancy. A literature search was conducted on PubMed, WHOLIS, PAHO and Cochrane library. Only intervention studies were considered for inclusion and data were combined by meta-analyses if available from more than one study. Sixteen intervention studies were included in the review. Pooled analysis showed a positive impact of balanced protein-energy supplementation on birthweight compared with control [mean difference 73 (g) [95% confidence interval (CI) 30, 117]]. This effect was more pronounced in undernourished women compared with adequately nourished women. Combined data from five studies showed a reduction of 32% in the risk of LBW in the intervention group compared with control [relative risk (RR) 0.68 [95% CI 0.51, 0.92]]. There was a reduction of 34% in the risk of small-for-gestational-age babies in the intervention compared with the control group [RR 0.66 [95% CI 0.49, 0.89]]. The risk of stillbirth was also reduced by 38% in the intervention group compared with control [RR 0.62 [95% CI 0.40, 0.98]]. In conclusion, balanced protein-energy supplementation is an effective intervention to reduce the prevalence of LBW and small-for-gestational-age births, especially in undernourished women.

Keywords: *Pregnancy*, *nutrition*, *protein*, *low birth weight*, *undernourished*, *small for gestational age*.

The nutritional status of a woman before and during pregnancy is important for a healthy pregnancy outcome.[1] Maternal malnutrition is a key contributor to poor fetal growth, low birthweight (LBW) and infant morbidity and mortality and can cause long-term, irreversible and detrimental cognitive, motor and health impairments.[2–4] Undernutrition in females may occur during childhood, adolescence and pregnancy, and has a cumulative adverse impact on the birthweight of future babies.[2]

This review will discuss the following aspects of maternal nutrition:

1 an historical background of famine studies to describe the association between maternal malnutrition and birth outcomes (mostly observational studies);
2 to assess the effect of balanced protein-energy supplementation during pregnancy on pregnancy outcomes (experimental studies).

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Famine studies

During the World War II, several studies were carried out in the Netherlands Leningrad and Germany, and knowledge about maternal malnutrition and its relation with birth outcomes mostly derived from these studies. The common aspect in all these studies was that there was an acute shortage of food as a result of war. Table S1 provides a brief description of famine studies that reported data on maternal nutrition and birth outcomes.

The Dutch famine lasted 6 months during the winter of 1944–45.[5–7] The food intake of mothers was markedly decreased as the official rations fell as low as 590 calories a day. This food rationing resulted in maternal weight loss of as much as 2.5 kg from pre-famine levels. The birthweight was also affected and the mean birthweight fell by about 300 g at the height of the famine.[5] The greatest effects on birthweight were among infants conceived before the onset of, but delivered during, the famine.[5,6] Women in their third trimester of pregnancy were affected the most and there was little difference in impact between those exposed to the famine only during the third trimester and those exposed during both the second and the third trimesters. No adverse effect of famine was observed among infants conceived during, and exposed to, famine through the second trimester but whose mothers received inadequate nutrition during the third trimester. During the height of famine, perinatal mortality rates were raised sixfold, from about 4 per 1000 to as high as 24 per 1000 births. A recent study by Stein *et al*. showed that infants exposed to intrauterine famine may be predisposed to the development of hypertension, obesity and diabetes mellitus in middle age.[8]

Data from the famine in Leningrad, the former Soviet Union was reported by Antonov.[9] The siege in Leningrad was extremely severe and of longer duration. It lasted from August 1941 to January 1943, while the worst period was from September 1941 to February 1942. Food intake was markedly decreased as bread rations fell to 250 g per day among manual and 125 g per day among non-manual workers. A review of data from one of the clinics showed that mean birthweight of liveborn infants during the famine was 2789 g, a decrease of almost 550 g. Perinatal mortality was substantially high as over a quarter of babies died during January–June 1942.[10]

There was a shortage of food in many parts of Germany, after the end of World War II. Data from a town named Wuppertal, Germany were reported by Dean.[11] The siege in Germany was not as severe as those in Holland and Leningrad. Official rations fell as low as 1052 kcal a day. Data from one clinic showed that during the worst deprivation, mean birthweight was lower, on average, by 170 g among private patients and by 227 g among public patients. This decrease was later reversed; when official rations were as high as 1550 kcal per day, birthweight drop was, on average, 81 g among private patients and 117 g among public patients.[11]

Very recently, Huang *et al*. reported data from the Chinese Famine (1959–61).[12] The Chinese Famine was much longer and more severe than those described above. It is considered to be one of the longest in human history, causing up to 30 million deaths.[13] Although all parts of China were affected by famine, its severity and duration varied across different areas. In rural areas affected by famine, birthweights were greater by 72 g in the famine group than the offspring of women born in 1963 and unexposed to the famine. There was no association of famine with offspring birth size in urban areas. The authors proposed that markedly increased mortality in rural areas may have resulted in the selection of hardier mothers with greater growth potential, which becomes expressed in their offspring.[12]

In conclusion, acute severe maternal malnutrition may adversely affect the birthweight of the fetus especially when the exposure is during the third trimester of the pregnancy. There appears to be an increased risk of perinatal mortality when there is exposure to intrauterine famine and the risk may be as high as sixfold in comparison with those not exposed to famine.

Effect of balanced protein-energy supplementation during pregnancy on birth outcomes

This section will focus on a review of studies on macronutrient food supplementation for pregnant women. During pregnancy extra energy is required for the growth of the fetus, placenta and various maternal tissues, such as in the uterus, breast and the fat stores.[14] The ideal situation for a woman is to enter pregnancy with a normal weight and good nutritional status. Pre-pregnancy weight is a strong predictor for LBW.[1] Major determinants for LBW in low- and middle-income countries are poor maternal nutritional status [low body mass index (BMI)] at conception, inadequate gestational weight gain due to poor dietary intake and short maternal stature due to mother's own childhood undernutrition.[15]

Differences in the body size, life style and nutritional status of the mother[3,16] underscore the need for population-specific estimates of energy requirements and recommendations for energy intake of a pregnant woman. Several nutrition interventions have been proposed and evaluated in accordance with the maternal needs during pregnancy.[17] Some of these include dietary advice to pregnant women (as discussed in another paper in this supplement), balanced protein/energy supplementation (protein provides <25% of total energy content), high protein (the protein provided 25% of the total energy content), isocaloric protein supplementation (the protein replaces an equal quantity of non-protein energy) and prescribing low-energy diet to pregnant women who either are overweight or exhibit high weight gain earlier in gestation.[17–19] Among these interventions, balanced protein-energy supplementation is considered as one of the most promising macronutrient interventions in prevention of adverse perinatal outcomes including intrauterine growth restriction.[17,20]

Studies from the UK[21,22] and Chile[23] found that there was no positive effect on pregnancy outcomes when maternal energy intakes were isocalorically replaced with 10–11% of protein. Even higher levels of protein supplementation (>25% of energy) in relatively well-nourished populations did not show any benefits on pregnancy outcomes.[24,25] Findings from a recent meta-analysis by Kramer and Kakuma[20] also showed no effect of unbalanced protein supplementation on pregnancy outcomes like birthweight and small-for-gestational-age babies. Balanced protein-energy supplementation is designed to provide less than 25% of total energy content and is believed to be the most suitable supplement for malnourished pregnant women. In this section we review data from intervention studies examining balanced protein-energy supplementation during pregnancy and its effects on adverse birth outcomes.

Methods

To assess the effect of balanced protein-energy supplementation, a literature search was performed on different electronic databases. The search strategies used in different databases are given in Appendix S1. We synthesised the collective evidence from different interventional studies with the help of meta-analysis.

Inclusion and exclusion criteria

- Balanced protein-energy supplementation was defined as nutritional supplementation during pregnancy in which protein provided less than 25% of the total energy content.
- Those studies were excluded where the main intervention was dietary advice to pregnant women for increase in protein/energy intake, high protein supplementation (i.e. supplementation in which protein provides at least 25% of total energy content), isocaloric protein supplementation (where protein replaces an equal quantity of non-protein-energy content) or low energy diet to pregnant women who either are overweight or exhibit high weight gain earlier in gestation.
- Only intervention studies (randomised, quasi-randomised trials and before after design) were included in the meta-analysis.
- The comparison group include either routine diet or no intervention.

Quantitative data synthesis

The primary outcomes of interest included LBW, small-for-gestational age and mean birthweight (g). We abstracted data on other neonatal and maternal outcomes including neonatal mortality, stillbirth, birth length, head circumference, pre-eclampsia, gestational weight gain/week and Bayley mental score at 1 year. The summary estimates from the meta-analyses were presented as relative risk (RR) for dichotomous data and mean difference (MD) for continuous data along with their corresponding 95% confidence interval (CI). Assessment of statistical heterogeneity in the pooled data was done by visual inspection of forest plots, by the chi-square (*P*-value) and by calculating the I^2 statistic [calculated as $I^2 = (Q - \text{d.f.})/Q$, where Q is Cochrane's heterogeneity statistic and d.f. is the degrees of freedom]. Heterogeneity was assumed to be substantial when the *P*-value of chi-square test was <0.10, and/or I^2 exceeded 50%. Reasons for heterogeneity were explored by doing a sensitivity analyses that included removing studies with large attrition and/or small sample size.

Estimates of pooled effect measures were generated from either the fixed-effects models or the random-effects models, the latter used when there was substantial heterogeneity across the pooled studies ($I^2 \geq 50\%$). Data from cluster randomised trials were pooled with individually randomised trials. In this case, cluster adjusted values were used as given in the original study; however, if results were not adjusted for cluster randomisation, sample sizes were adjusted by using an estimate of the intracluster correlation coefficient derived from the trial, or inferred from similar studies.[26]

All analyses were conducted using software Review Manager version (version 5).[27] The quality of overall evidence was assessed by GRADE criteria.[28] According to this grading system, the quality of overall evidence was graded as 'high', 'moderate', 'low' or 'very low'. A score of 'high' means that further research is very unlikely to change the results of the intervention. A score of 'moderate' means further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate, and a score of 'low' means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. A score of 'very low quality' means that we are very uncertain about the estimate.[28]

Results

Figure 1 shows the results of literature search. We identified 5606 titles from searches conducted on all databases. After screening the titles and abstracts, 24 studies were identified that addressed protein-energy supplementation during pregnancy. A total of 16 interventional studies were chosen for data extraction to conduct meta-analyses.[21–23,25,29–40] Table 1 presents the characteristics of included studies. Nine studies were excluded and the reasons for exclusion are provided in Table 2. Eight of the included studies were from developing countries[30–32,34,35,37,38,40] and eight were from developed countries.[21–23,25,29,33,36,39] In 10 of the included studies, women were undernourished (as defined by authors) and/or were at risk of delivering a LBW baby.[23,25,29,31,34–36,38,39,41]

Sixteen studies reported data on birthweight and the pooled estimate showed that babies born to women who received balanced protein-energy

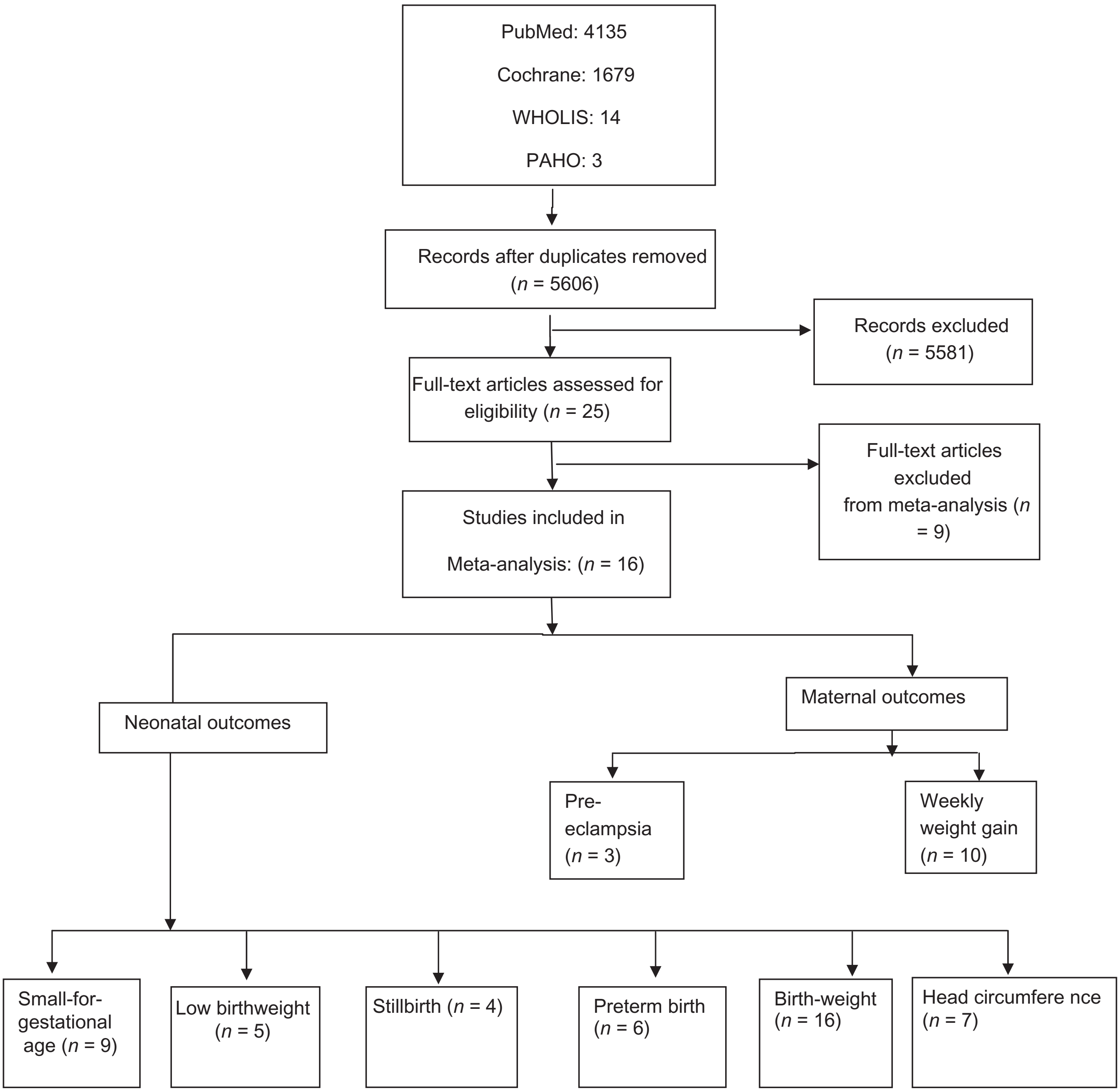

Figure 1. Flow diagram for identification of interventional studies evaluating balanced protein-energy supplementation during pregnancy.

Table 1. Characteristics of studies included in the meta-analyses

Study ID	Country	Population	Intervention	Comments
Blackwell 1973[31]	Taiwan	Women in the last trimester of pregnancy with at least one male child planned to have at least one additional child, and were judged to be of low socio-economic status. All subjects were consuming baseline protein <40 g/day	RCT. Supplement: Chocolate-flavoured liquid. Total energy: 800 kcal energy containing 40 g protein plus vitamins/minerals. Control: Vitamins and minerals only	Methods of sequence generation and allocation concealment were not described explicitly. Supplement started after prior birth and continued during index pregnancy
Ceesay 1997[35]	Gambia	Rural population. Chronically undernourished women and this condition exacerbates during hungry season (June–October)	RCT. The supplement: 2 biscuits containing roasted groundnuts, rice flour, sugar and groundnut oil. Total energy content: 1017 kcal. Individual components: 22 g protein, 56 g fat, 47 mg calcium and 1.8 mg iron. Control: No supplement. Women in both the groups received antenatal care	Study continued for 5 years. 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). Results were cluster adjusted by assuming an intracluster correlation coefficient of 0.01. The formula used for calculating design effect was = 1 + (M − 1) intracluster correlation coefficient, where M is the mean cluster size. Supplementation was given daily and began at 20 weeks of gestation
Elwood 1981[33]	England	Study conducted in two towns of South Wales. One town was industrial and population was well off while other town consisted mostly of low-socio-economic-status population. Participants of this study were considered as adequately nourished	RCT. Supplement: Free tokens worth $^1/_2$ pint milk for each participant. Control: No intervention	Attrition was 24% with evidence of higher losses in control group. Control group also had higher percentage of smokers, for which no adjustment was done
Metcoff 1985[39]	USA	900 women attending the prenatal clinics at the Oklahoma Memorial Hospital (OMH = University Hospital) and eligible by Oklahoma women, infants, and children. Participants of this study were considered as malnourished	The participants received vouchers for supplements of milk, eggs and cheese, intended to provide 40–50 g protein and 900–1000 kcal daily in addition to regular diet	Attrition and exclusion included 16% of the study participants
Mora 1978[32]	Colombia	Women in the first or second trimester of pregnancy. Women were selected from a poor community and had at least 50% of previous children whose weight-for-height < 85% of Colombian standard. Participants of this study were considered as malnourished	RCT. Supplement: 60 g dried skim milk, 150 g enriched bread and 20 g vegetable oil. Total energy: 856 kcal. Control: No intervention	Methods of randomisation and allocation concealment not described. Supplement started in the third trimester. Data on term LBW used in analysis of small-for-gestational age
Rush 1980[25]	USA	Low-income black, English-speaking women at risk for low birthweight. The risk of low birthweight was based on: (1) pre-pregnancy weight < 110 lbs; (2) pre-pregnancy weight 110–139 lbs plus low gestational weight gain as of recruitment; (3) pre-pregnancy weight 110–139 lbs plus previous history of LBW; (4) pre-pregnancy weight 110–139 lbs plus protein intake < 50 g in the 24-h preceding registration. Participants of this study were considered as malnourished	RCT. Two experimental groups: Complement: A beverage of 16-oz containing 322 kcal energy, 6 g protein and vitamins/minerals (balanced protein-energy). Supplement: A 16-oz beverage containing 470 kcal + 40 g protein per day + vitamins and minerals (high protein-energy). Control: supplement containing vitamins/minerals only. (Analysis included in our review is that of complement vs. control)	Methods of sequence generation were not reported. Allocation concealment was inadequate. No reason given for 25% missing data. Risk of LBW (as recruitment criteria) was 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; (3) pre-pregnancy weight 110–139 lbs plus previous history of low birthweight; (4) pre-pregnancy weight 110–139 lbs plus protein intake < 50 g in the 24-h preceding registration
Girija 1984[34]	India	Poor Indian women in third trimester of pregnancy. Participants of this study were considered as malnourished	RCT. Supplement: 50 g sesame cake, 40 g jaggery and 10 g oil. Total energy: 417 kcal. Control: Routine diet	Allocation concealment inadequate
Atton 1990[29]	England	Trial was conducted on a subset of Asian women with triceps skinfold increase ≤2 mm from 18 to 28 weeks. Participants of this study were considered as malnourished	RCT. Supplement: flavoured milk. Total energy: 407 kcal. Total protein: 14.6 g. Control: Routine diet	Methods of sequence generation by alternative allocation. Allocation concealment was inadequate. In the Method section it was described that there was alternative allocation; however, numbers of women were equal in both treatment groups after excluding non-compliers. Slight discrepancy in mean birthweight data in tables 4 vs. 5

Huybregts 2009[40]	Burkina Faso	Pregnant females in the study area. Participants of this study were considered as malnourished	RCT. The fortified food supplement intervention group was given a fortified spread consisting of 33% peanut butter, 32% soy flour, 15% vegetable oil, 20% sugar, and a multiple micronutrient cocktail providing the Recommended Daily Allowance for pregnant women. Control: Multiple micronutrient only	Methods of sequence generation by computer. Adequate allocation concealment. Disaggregated data available for malnourished women and used accordingly for birthweight analysis
Kaseb 2002[37]	Iran	53 healthy mothers who were neither addicts nor on medication and were free from medical disorders. Participants of this study were considered as adequately nourished	The experimental group received traditional food (rice-milk porridge, lentils, poltage, cheese, yogurt, eggs and milk with bread), supplying an extra 400 kcal energy and 15 g protein from the fourth month of pregnancy until childbirth	Relatively small sample size
Mardones-Santander 1988[23]	Chile	Pregnant females who are were underweight, meaning that the initial weight for height at the first prenatal visit (at mean gestational age of 14 weeks) was below that recommended for women who weigh < 95% of the standard at week 12 of gestation. Other inclusion criteria included: age > 18 years, parity 0–5, <20 weeks pregnant according to date of last menstrual period, non-smoking, non-alcoholic-consuming. Women with multiple pregnancies were excluded at delivery. Participants of this study were considered as malnourished	RCT. There were two intervention groups, PUR and V-N: The PUR group received powdered milk (an isocaloric supplement) while V-N group received a fortified formula milk (a balanced protein-energy supplement)	Sequence generation by alternative allocation. Unclear information of allocation concealment. We included the data for comparison between V-N group and the non-consumers
Prentice 1987[38]	Gambia	All the pregnant females living in the study area. In the study area because of low rainfall, harvests were rarely sufficient to last the entire year and a hungry season develops between July and September	Before and after design. Supplement: Energy, 468 and 78 kcal; protein, 17.4 and 2.9 g; fat, 25.5 and 1.6 g; calcium, 180 and 95 mg; riboflavin, 0.23 and 0.24 mg; vitamin A, 0 and 340 µg; vitamin C, 0 and 10 mg	The supplement was prepared with the help of local villagers and was distributed every day except Sunday
Ross 1985[30]	South Africa	Black women < 20 weeks of gestation. Participants of this study were considered as adequately nourished	RCT. Supplement: Two 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. Total energy: 700–800 kcal. Total protein: 36–44 g protein. Control: Placebo pills	Methods of sequence generation by alternative allocation. Allocation concealment was inadequate. No data presented on compliance or substitution. Number of women originally randomised not reported. Neither original sample size not given nor its justification. Zinc-supplemented group is excluded from review
Campbell Brown 1983[36]	Scotland	Aberdeen primiparous women at high risk of low birthweight delivery starting approximately at 27-week gestation. Risk of LBW was based on low maternal height, weight or weight-for-height at 20 weeks, or weight gain between 20 and 30 weeks. Participants of this study were considered as malnourished	RCT. Supplement: pint flavoured milk drink or 1 pint fresh milk, or 75 g cheddar cheese. Total energy: 300 kcal energy. Total protein: 15–20 g. Control: Routine diet.	Strict alternative allocation; however, inadequate allocation concealment.
Viegas 1982[22]	England	Asian women in Birmingham, UK <20 weeks of gestation who appeared well nourished based on their weight and height. Participants of this study were considered as adequately nourished	RCT. Supplement: Flavoured carbonated glucose drink plus vitamins from 18 to 38 weeks. Total energy: 273 kcal energy (with 11% of energy as protein). Control: Supplement of flavoured carbonated water containing iron and vitamin C	Methods of sequence generation by alternative allocation. Allocation concealment was inadequate. Designed as 3-arm trial, but group receiving supplement with 11% of energy provided as protein combined with energy-only group for this review. Results presented only in graphic form; extracted data are therefore approximate
Viegas 1982[21]	England	Asian women, <20 weeks of gestation (who appeared well-nourished prior to pregnancy, but 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)	RCT. 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. Control: Supplement of flavoured carbonated water containing iron and vitamin C	Methods of sequence generation by alternative allocation. Allocation concealment was inadequate. Designed as 3-arm trial, but group receiving supplement with 10% of energy provided as protein combined with energy-only group for this review. Data from intention-to-treat analysis extracted from graph; not presented in tabular form

RCT, randomised controlled trial; LBW, low birthweight.

Table 2. Characteristics of excluded studies from meta-analyses

Study ID (reference)	Reason for exclusion
Kardjati 1988[43]	Both the groups received the nutrition supplement
Lechtig 1975[46]	The control group received a low-energy drink
Anderson 1995[47]	Nutritional education only
Briley 2002[48]	Nutritional education only
Hankin 1962[49]	Nutritional education only
Hunt 1976[50]	Nutritional education only
Kafatos 1989[51]	Nutritional education only
Sweeney 1985[52]	Nutritional education only
Iyengar 1967[24]	Isocaloric protein-energy supplementation
Rasmussen 2010[53]	High protein-energy supplement

supplementation had a higher birthweight compared with controls (MD 73 [95% CI 30, 117]) (Figure 2). There was a substantial heterogeneity in the pooled data ($I^2 = 80\%$) and thus the random-effects models were used. A subgroup analysis based on nutritional status of the mothers showed that balanced protein-energy supplementation was more effective in malnourished women (MD 100 [95% CI 53, 147]) than adequately nourished women (MD 37 [95% CI –34, 99]). Data on the incidence of LBW (birthweight <2500 g) were available from five studies and the pooled results showed that balanced protein-energy supplementation resulted in a 32% reduction in LBW prevalence in the intervention compared with the control group (RR 0.68 [95% CI 0.51, 0.92]) (Figure 3). Random-effects models were used as there was heterogeneity in the pooled data ($I^2 = 52\%$).

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Malnourished women								
Atton 1990[29]	3130	374	87	3190	402	61	5.0%	-60.00 [-187.88, 67.88]
Blackwell 1973[31]	3082.13	400	55	2941.93	306	55	4.8%	140.20 [7.10, 273.30]
Campbell Brown 1983[36]	3032	372	90	2995	395	90	5.6%	37.00 [-75.10, 149.10]
Ceesay 1997[35]	2966	422	620	2860	427	553	8.0%	106.00 [57.32, 154.68]
Girija 1984[34]	2939	376	10	2676	451	10	1.2%	263.00 [-100.93, 626.93]
Huybregts 2009[40]	2916	408	64	2810	480	54	3.9%	106.00 [-56.42, 268.42]
Mardones-Santander 1988[23]	3178	483	391	2990.7	340.2	38	5.3%	187.30 [69.01, 305.59]
Metcoff 1985[39]	3234	90	238	3059	90	172	8.7%	175.00 [157.35, 192.65]
Mora 1978[32]	2978	377	207	2927	392	200	7.0%	51.00 [-23.76, 125.76]
Prentice 1987[38]	2997	378.9	197	2880	119.6	182	7.7%	117.00 [61.31, 172.69]
Rush 1980[25]	3011	508	256	2970	535	264	6.4%	41.00 [-48.65, 130.65]
Viegas 1982[21]	3184	540	31	3027	255	14	2.5%	157.00 [-75.33, 389.33]
Subtotal (95% CI)			**2246**			**1693**	**66.2%**	**100.86 [56.14, 145.58]**
Heterogeneity: Tau² = 3318.27; Chi² = 39.93, df = 11 (P < 0.0001); I² = 72%								
Test for overall effect: Z = 4.42 (P < 0.00001)								
1.4.2 Adequately Nourished women								
Blackwell 1973[31]	3184	335	57	3189.93	333	56	5.2%	-5.93 [-129.10, 117.24]
Elwood 1981[33]	3378	519	591	3325	498	562	7.6%	53.00 [-5.70, 111.70]
Huybregts 2009[40]	2945	463	457	2947	425	439	7.6%	-2.00 [-60.16, 56.16]
Kaseb 2002[37]	3300	400	28	3080	310	25	3.2%	220.00 [28.38, 411.62]
Ross 1985[30]	3229	432	62	3171	483	33	3.1%	58.00 [-138.77, 254.77]
Viegas 1982[22]	3028	431	97	3060	472	45	3.9%	-32.00 [-194.40, 130.40]
Viegas 1982[21]	3115	454	56	3233	433	27	3.0%	-118.00 [-320.03, 84.03]
Subtotal (95% CI)			**1348**			**1187**	**33.8%**	**22.58 [-27.17, 72.32]**
Heterogeneity: Tau² = 1180.33; Chi² = 8.42, df = 6 (P = 0.21); I² = 29%								
Test for overall effect: Z = 0.89 (P = 0.37)								
Total (95% CI)			**3594**			**2880**	**100.0%**	**73.78 [30.42, 117.15]**
Heterogeneity: Tau² = 5530.95; Chi² = 88.87, df = 18 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 3.33 (P = 0.0009)								

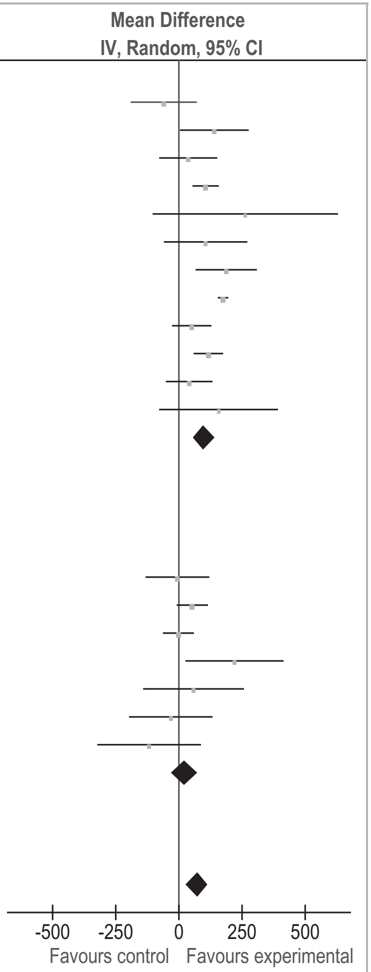

Figure 2. Effect of balanced protein-energy supplementation on birthweight (g).

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blackwell 1973[31]	7	143	11	138	8.5%	0.61 [0.25, 1.54]
Ceesay 1997[35]	112	1010	176	1037	35.8%	0.65 [0.52, 0.81]
Huybregts 2009[40]	67	523	67	497	29.7%	0.95 [0.69, 1.30]
Mardones-Santander 1988[23]	24	391	5	72	8.3%	0.88 [0.35, 2.24]
Prentice 1987[38]	16	200	37	185	17.6%	0.40 [0.23, 0.69]
Total (95% CI)		**2267**		**1929**	**100.0%**	**0.68 [0.51, 0.92]**
Total events	226		296			

Heterogeneity: Tau² = 0.05; Chi² = 8.26, df = 4 (P = 0.08); I² = 52%
Test for overall effect: Z = 2.51 (P = 0.01)

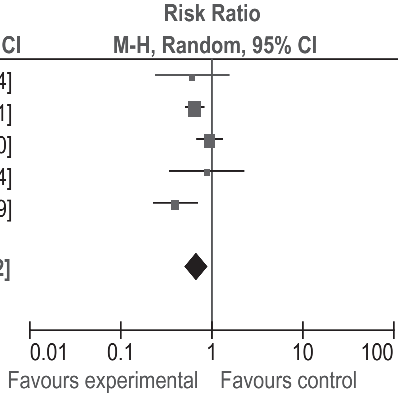

Figure 3. Effect of balanced protein-energy supplementation on risk of low birthweight. M-H, Mantel-Haenszel.

Pooled results from nine studies reporting data on the prevalence of small-for-gestational age showed a reduction of 34% in the intervention compared with the control (RR 0.66 [95% CI 0.49, 0.89]) (Figure 4). As the pooled estimate had significant heterogeneity ($I^2 = 87\%$), random-effects models were used. The risk of stillbirth in the intervention group was 38% lower based on pooled data from three studies (RR 0.62 [95% CI 0.40, 0.98]) (Figure 5). Balanced protein-energy supplementation had virtually no effect on preterm birth rates (Figure 6). Table 3 shows summary estimates of some of the other maternal and neonatal outcomes. Table 4 shows 'summary of findings' table for selected outcomes according to the GRADE criteria.

Comments

The effects of balanced protein-energy supplementation during pregnancy on adverse birth outcomes have been evaluated before, including a Cochrane review[20] and the other being a review for the Live Saved Tool (LiST) model.[42] Our results are in accordance with these reviews with some additions and modifications for certain outcomes. We updated literature search and used slightly different inclusion/exclusion criteria by including quasi-experimental trials and before–after studies. This led to the inclusion of five more studies compared with the previous reviews.[23,37–40] Two of these studies were randomised trials,[23,40] two were quasi-randomised[37,39] and one was

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Blackwell 1973[31]	6	94	10	88	6.1%	0.56 [0.21, 1.48]
Ceesay 1997[35]	69	620	94	553	14.3%	0.65 [0.49, 0.87]
Elwood 1981[33]	25	591	27	562	10.9%	0.88 [0.52, 1.50]
Girija 1984[34]	0	10	5	10	1.1%	0.09 [0.01, 1.45]
Huybregts 2009[40]	167	518	177	494	15.7%	0.90 [0.76, 1.07]
Mardones-Santander 1988[23]	126	391	61	72	15.7%	0.38 [0.32, 0.45]
Mora 1978[32]	12	177	14	162	8.2%	0.78 [0.37, 1.65]
Prentice 1987[38]	104	197	126	182	15.8%	0.76 [0.65, 0.90]
Rush 1980[25]	30	265	43	264	12.3%	0.70 [0.45, 1.07]
Total (95% CI)		**2863**		**2387**	**100.0%**	**0.66 [0.49, 0.89]**
Total events	539		557			

Heterogeneity: Tau² = 0.14; Chi² = 61.19, df = 8 (P < 0.00001); I² = 87%
Test for overall effect: Z = 2.69 (P = 0.007)

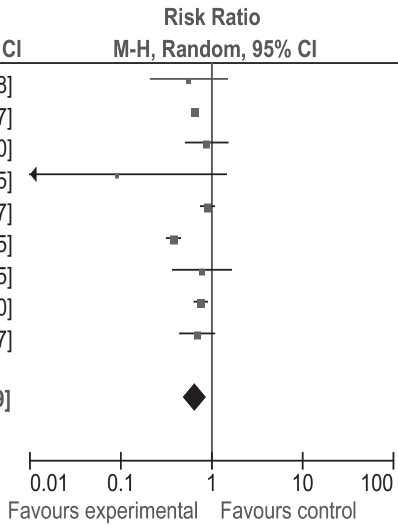

Figure 4. Effect of balanced protein-energy supplementation on risk of small-for-gestational-age baby. M-H, Mantel-Haenszel.

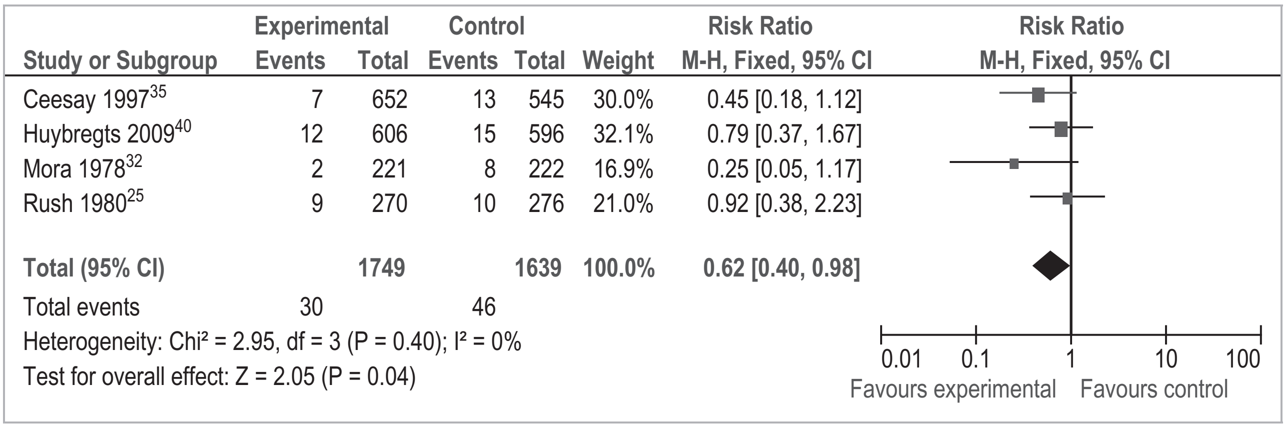

Figure 5. Effect of balanced protein-energy supplementation on risk of stillbirth. M-H, Mantel-Haenszel.

a before–after study.[38] Of the two new randomised trials included in this review, one is a new study[40] and the second was a previous study.[23] In the second study we had compared group of balanced protein-energy supplements with control (taken as those who were non-complier) instead of that with isocaloric protein-energy supplementation. In the review by Kramer and Kakuma,[20] this study has been included as that with isocaloric protein-energy supplementation. We have conducted a new meta-analysis for the prevalence of LBW that was not attempted before and have updated other outcomes.

Pooled data from 16 studies showed that balanced protein-energy supplementation has a positive impact

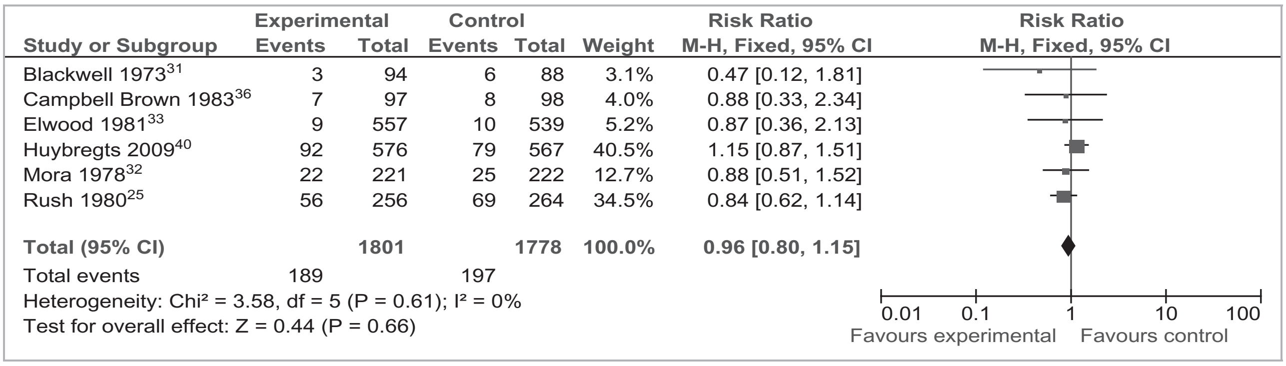

Figure 6. Effect of balanced protein-energy supplementation on risk of preterm birth. M-H, Mantel-Haenszel.

Table 3. Summary estimates of other maternal and neonatal outcomes

Outcome	No. of studies	No. of participants	Summary estimate	Fixed/random model
Neonatal mortality	4	3361	RR = 0.68 [0.59, 0.82]	Fixed
Pre-eclampsia	3	516	RR = 1.20 [0.77, 1.89]	Fixed
Gestational age (weeks)	9	3087	MD = –0.03 [–0.26, 0.21]	Random
Birth length (cm)	7	3698	MD = 0.16 [0.02, 0.31]	Fixed
Birth head circumference (cm)	7	3680	MD = 0.07 [–0.02, 0.16]	Fixed
Gestational weight gain/week (g)	10	2571	MD = 20.74 [1.46, 40.02]	Fixed
Bayley mental scores at 1 year	1	411	MD = –0.74 [–1.95, 0.47]	Fixed
Weight at 1 year (g)	2	623	MD = 30.43 [–139.67, 200.53]	Fixed

RR, relative risk; MD, mean difference.

Table 4. Results of pooled analysis and qualitative grading according to GRADE criteria

Quality assessment						Summary of findings		
				Directness		No. of events		Effect
No. of studies	Design	Limitations	Consistency	Generalisability to population of interest	Generalisability to intervention of interest	Intervention	Control	Relative risk [95% CI]
Outcome: Birthweight (g): Quality of evidence – moderate								
16	RCTs/cluster RCT/quasi-RCTs, before after design	Methods of sequence generation and allocation were inadequate in some of the included studies	Except three studies, all the studies showing a positive effect in favour of intervention. Significant statistical heterogeneity ($I^2 = 76\%$). Random models used	Studies conducted in both developed and developing countries. All the studies did not included undernourished women	Protein content of Supplement for intervention group ranged from 30 to 44 g per day. The protein content provided <25% of total energy content in all the studies	3594	2880	Mean difference 73.78 [30.42, 117.15]
Outcome: Small-for-gestational age: Quality of evidence – moderate								
9	RCTs/cluster RCT/quasi-RCTs, before after design	Two studies were quasi-experimental trial. Sequence generation and allocation concealment was not adequate in some of the included studies	All the studies showing a positive effect in favour of intervention. Significant statistical heterogeneity in the pooled data ($I^2 = 85\%$). $P = 0.005$. The sole contributor to this study was study by Mardones-Santander *et al*. 1988[23]	Studies conducted in both developed and developing countries. All the studies did not included undernourished women	Protein content of supplement for intervention group ranged from 30 to 44 g per day. The protein content provided <25% of total energy content in all the studies	2863	2387	Relative risk 0.68 [0.51, 0.92]
Outcome: Low birthweight (<2500 g): Quality of evidence – moderate								
5	RCTs/cluster RCT/quasi-RCTs, before after design	High risk of bias because of inadequate sequence generation and allocation concealment in one of the included studies. One of the studies had before after design	All the studies showing a positive effect in favour of the intervention. Significant statistical heterogeneity ($I^2 = 52\%$). Random models used	Studies conducted in both developed and developing countries. All the studies did not included undernourished women	Protein content of supplement for intervention group ranged from 30 to 44 g per day. The protein content provided <25% of total energy content in all the studies	226	296	Relative risk 0.68 [0.51, 0.92]
Outcome: Stillbirth: Quality of evidence – low								
3	RCTs/cluster RCT/quasi-RCTs, before after design	High risk of bias because of inadequate sequence generation and allocation concealment in one of the included studies	All the studies showing a positive effect in favour of the intervention. No significant statistical heterogeneity ($I^2 = 20\%$)	Studies conducted in both developed and developing countries. All the studies did not included undernourished women	Protein content of supplement for intervention group ranged from 30 to 44 g per day. The protein content provided <25% of total energy content in all the studies	18	31	Relative risk 0.55 [0.31, 0.97]
Outcome: Neonatal mortality: Quality of evidence – low								
3	RCTs/cluster RCT/quasi-RCTs	One quasi-experimental design. Allocation concealment was not adequate for one of the included cluster RCT. Large loss to follow-up in included studies	No heterogeneity ($I^2 = 0$). $P = 0.81$	One study from a developed country and two from developing countries	Protein content of supplement for intervention group ranged from 30 to 44 g per day. The protein content provided <25% of total energy content	23	33	Relative risk 0.63 [0.37, 1.06]

RCT, randomised controlled trial.

on birthweight (MD 73 [95% CI 30, 117]). Similar results were found in the LiST review (MD 59 g [95% CI 33, 86]); however, the results of Cochrane review were statistically non-significant (MD 37 [95% CI –0.21, 75]). The differences in the magnitude and statistical significance of the summary estimates in the current review compared with LiST and Cochrane review are the addition of five more studies[23,37–40] and exclusion of one study[43] included in the Cochrane but excluded in this review and also that in the LiST review. The main reason for exclusion of this study was that both the study groups received the supplement (high vs. low energy) and it was difficult to ascertain the true effect of the intervention.

The results of the pooled estimate on the prevalence of LBW were consistent with the positive impact on mean birthweight and maternal weekly gestational weight gain. Combined results from five studies showed that balanced protein-energy supplementation reduced the prevalence of LBW by 32%. This analysis was not attempted before and contributes an important data of the effectiveness of balanced protein-energy supplementation in reducing LBW in developing countries. Similarly, the prevalence of small-for-gestational age was also reduced by 44%. The direction of effect was the same as that of LiST and Cochrane review; however, the magnitude of effect was different because of addition of three more studies in this analysis.[23,38,40]

The included studies were of variable quality with most of the studies conducted in the 1980s and 1990s; the most recent study was conducted in 2002 in Iran.[37] Methods of randomisation and allocation concealment were inadequate in most of the studies. Even though the quality of methods varied across these studies, the direction and magnitude of effect was quite consistent. The qualitative assessment of the pooled estimates for birthweight and small-for-gestational-age babies was that of moderate level based on limitation of methods in some of the included studies.

Participants in 11 of the studies were categorised as malnourished as defined by the authors (Figure 2). In most of the studies this assessment was based on general nutritional status of the study population. Only five of studies used defined criteria to recruit women who were undernourished or were at risk of having a LBW baby.[22,23,25,32,44] The criteria used across these studies included, for example, pre-pregnancy weight, low weight-for-height, history of a LBW baby, low maternal weight gain and triceps skinfold thickness. None of the studies used BMI as the recruitment criterion. In any case, the subgroup analysis based on nutritional status of the mothers showed that balanced protein-energy supplementation was more effective in malnourished women (MD 100 [95% CI 53, 147]) than adequately nourished (as defined by authors) women (MD 37 [95% CI –34, 99]). It can therefore be inferred from this analysis that a food supplement with balanced protein-energy content seems the most suitable intervention for malnourished women to increase birthweight and can subsequently reduce the risk of LBW and small-for-gestational-age babies in these women. This finding should; however, be interpreted carefully as most of the studies did not use a defined criterion to define undernourished women and no study used low BMI as the inclusion criterion. The implementation of intervention should also be considered according to the social, cultural and economic context of the target population.

The fact that most of the studies did not used standardised criteria to define undernourished women calls for future studies with more rigorous inclusion criteria and improved methods for conduct of the studies. Another important consideration for future research is the combination of balanced protein-energy with micronutrient supplementation. A recent review by our team for the LiST[45] has shown that multiple micronutrient supplementations can reduce incidence of small-for-gestational-age babies by 9%. A recent study from Burkina Faso has shown that combined supplementation with balanced protein-energy and appropriate multiple micronutrients has more pronounced effect on birth length than multiple micronutrients alone.[40] Future studies should be encouraged to replicate these findings in other parts of the world.

In conclusion, balanced protein-energy supplementation seems an effective intervention to reduce the risk of LBW and small-for-gestational-age births, especially in undernourished women in underdeveloped countries.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Description of famine studies.
Appendix S1. Search strategies used to identify studies addressing balanced protein-energy supplementation during pregnancy.

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