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Impact of macronutrient supplements for children born preterm or small for gestational age on developmental and metabolic outcomes: A systematic review and meta-analysis

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Data Availability Statement: Data and associated documentation are available to other users under the data sharing arrangements provided by the Maternal and Perinatal Research Hub, based at the Liggins Institute, University of Auckland (https://wiki.auckland.ac.nz/researchhub).The data dictionary and metadata will be published on the University of Auckland's data repository Figshare, which allocates a DOI and thus makes these details searchable and available indefinitely. Researchers

Abstract

Background

Nutritional supplements may improve development of infants born small (preterm or small for gestational age [SGA]) but may increase the risk of later metabolic disease. We conducted a systematic review and meta-analysis to assess the effects of macronutrient supplements for infants born small on later development and metabolism.

Methods and findings

We searched OvidMedline, Embase, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews from inception to April 1, 2019, and controlled-trials.com, clinicaltrials.gov, and anzctr.org.au. Randomised or quasirandomised trials were included if the intention was to increase macronutrient intake to improve growth or development of infants born small and assessed post-discharge outcomes. Co-primary outcomes were cognitive impairment and metabolic risk, evaluated in toddlers (<3 years), childhood (3 to 8 years), and adolescence (9 to 18 years). Two reviewers independently extracted data. Quality was assessed using the Cochrane Risk of Bias tool, and data were pooled using random-effect models.

Twenty-one randomised and one quasirandomised trial of variable methodological quality involving 3,680 infants were included. In toddlers born small, supplementation did not alter cognitive impairment (relative risk [RR] 1.00; 95% confidence interval [CI] 0.67 to 1.49; $P = 0.99$), and there were no differences in cognitive scores (mean difference [MD] 0.57; 95% CI −0.71 to 1.84; $P = 0.38$) or motor scores (MD 1.16; 95% CI −0.32 to 2.65; $P = 0.12$) between supplemented and unsupplemented groups. However, fewer supplemented children had motor impairment (RR 0.76; 95% CI 0.62 to 0.94; $P = 0.01$). In subgroup analyses, supplementation improved cognitive scores in boys (MD 5.60; 95% CI 1.07 to 10.14; $P = 0.02$), but not girls born small (MD −2.04; 95% CI −7.04 to 2.95; $P = 0.42$), and did not alter cognitive or motor scores in the subgroup of children born SGA. In childhood, there was no

are able to use this information and the provided contact address (researchhub@auckland.ac.nz) to request a de-identified dataset through the Data Access Committee of the Liggins Institute. Data will be shared with researchers who provide a methodologically sound proposal and have appropriate ethical approval, where necessary, to achieve the research aims in the approved proposal. Data requestors are required to sign a Data Access Agreement that includes a commitment to using the data only for the specified proposal, not to attempt to identify any individual participant, a commitment to secure storage and use of the data, and to destroy or return the data after completion of the project. The Liggins Institute reserves the right to charge a fee to cover the costs of making data available, if needed, for data requests that require additional work to prepare.

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Abbreviations: BMI, body mass index; CA, corrected age; CI, confidence interval; DASII, Developmental Assessment Scales for Indian Infants-Edition II; DBP, diastolic blood pressure; GDT, Guideline Development Tool; GMDS, Griffiths Mental Development Status; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HDL, high-density lipoprotein; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; IPD, individual participant data; IV, inverse variance; LDL, low-density lipoprotein; MAP, mean arterial pressure; MD, mean difference; M-H, Mantel-Haenszel; PMA, post-menstrual age; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; RR, relative risk; SBP, systolic blood pressure; SD, standard deviation; SGA, small for gestational age; SMD, standard mean difference; WISC, Wechsler Intelligence Scale for Children.

difference in cognitive impairment (RR 0.81; 95% CI 0.26 to 2.57; $P = 0.72$) or cognitive scores (MD 1.02; 95% CI −1.91 to 3.95; $P = 0.50$) between supplemented and unsupplemented groups. There were also no differences in blood pressure, triglyceride, and low-density lipoprotein (LDL) concentrations (all $P > 0.05$). However, supplemented children had lower fasting glucose (mmol/L: MD −0.20; 95% CI −0.34 to −0.06; $P = 0.005$) and higher high-density lipoprotein (HDL) concentrations (mmol/L: MD 0.11; 95% CI 0.02 to 0.19; $P = 0.02$). In subgroup analyses, there was no evidence of differences in blood pressure between supplemented and unsupplemented groups in boys or girls born small, or in SGA children. In adolescence, there was no difference between supplemented and unsupplemented groups in blood pressure, triglycerides, LDL and HDL concentrations, fasting blood glucose, insulin resistance, and fasting insulin concentrations (all $P > 0.05$). Limitations include considerable unexplained heterogeneity, low to very low quality of the evidence, and limited data beyond early childhood.

Conclusions

In this systematic review and meta-analysis of randomised trials, we found no evidence that early macronutrient supplementation for infants born small altered later cognitive function, although there was some evidence that supplementation may decrease motor impairment in toddlers. Contrary to the findings from observational studies, evidence from randomised trials suggests that early macronutrient supplementation for infants born small improves some metabolic outcomes in childhood.

PROSPERO registration

CRD42019127858.

Author summary

Why was this study done?

- Preterm and small-for-gestational-age (SGA) infants are at increased risk of poor growth, delayed development, and disability.
- Nutritional supplements are often given to these infants to improve growth and development, but observational studies suggest that this may lead to later increased risk of metabolic disease.
- The balance of these potential later benefits and risks is not known, and it is possible that they may be different in girls and boys.

What did the researchers do and find?

- We undertook a systematic review and meta-analysis of 21 randomised clinical trials and 1 quasirandomised trial of nutritional supplements involving 3,680 infants born preterm or SGA.

- We found that early supplements given to infants born small did not alter overall cognitive function, but in toddlers, early supplements decreased motor impairment and improved cognitive scores in boys.
- Some markers of risk of metabolic disease were improved after early nutritional supplements.

What do these findings mean?

- Early nutritional supplements for infants born preterm or small have little overall benefit for cognitive development but also do not appear to increase metabolic risk.
- These findings from randomised trials are in contrast to those from previous observational studies.
- Despite large numbers of trials involving thousands of infants, there is still limited evidence about the benefits and risks of early nutritional supplements after early childhood.

Introduction

Infants born preterm or small for gestational age (SGA) are at increased risk of poor growth, developmental delay, and disability [1–4]. As adults, they are at increased risk of obesity, diabetes, and cardiovascular disease [5]. Providing preterm and SGA infants with higher protein and energy intake during the first few weeks after birth has been associated with improved short-term growth and better developmental outcomes from infancy to adolescence [6–12]. However, observational data suggest that there may be important tradeoffs between early cognitive development and later metabolic diseases in preterm infants [13]. Rapid body mass index (BMI) gain and linear growth are associated with better cognitive development but at the expense of increased risk for adiposity and metabolic and cardiovascular disease in adulthood [14,15]. There is also limited evidence that these effects may differ in girls and boys [16].

Three previous systematic reviews have compared the effect of supplemented versus unsupplemented formula started after hospital discharge, fortified versus unfortified breastmilk started in hospital or after hospital discharge [11,17,18]. None of these reviews reported developmental outcomes after 18 months of age, and none reported long-term metabolic outcomes or assessed potential sex-specific effects.

We therefore undertook a systematic review and meta-analysis to assess the published data from randomised trials on the effects of early macronutrient supplements fed to preterm and SGA infants on developmental and metabolic outcomes after hospital discharge, and also whether these effects differed in girls and boys.

Methods

We used Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and registered this review prospectively in PROSPERO (registration number CRD42019127858).

Search strategy and selection criteria

We searched OvidMedline, Embase, Cochrane Library Central Registry of Controlled Trials, and Cochrane Database of Systematic Reviews from inception to April 1, 2019. We

searched for eligible ongoing trials in Current Controlled Trials (www.controlled-trials.com), Clinical Trials (www.clinicaltrials.gov), and the Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au). Conference abstracts were included if they provided usable data.

Inclusion criteria were as follows: (1) randomised controlled trials (RCTs) and quasi-RCTs without restrictions on date of publication or language; (2) infants born preterm (<37 weeks' gestation) or small (birth weight <2.5 kg or <10th centile); (3) the intervention was intended to increase intake of one or more macronutrients (protein, carbohydrate, fat, energy, or protein to energy ratio) with the primary aim of improving growth or development (interventions could be enteral, parenteral, or both; commence any time during initial hospitalisation after birth or after discharge; and must have been provided for ≥1 week); and (4) reported any of the prespecified outcomes (S1 Appendix) assessed after term equivalent age (>37 weeks' gestation) or after discharge from hospital after birth.

Studies that reported comparisons between unsupplemented and supplemented nutrition with parenteral supplements, human breast milk supplements, formula milk, or other macronutrients were eligible for inclusion. We excluded trials comparing the timing of the introduction of nutrition (early versus delayed feeding); macronutrients of different composition (e.g., different types of lipids or proteins); variations in intakes of micronutrients (including sodium, potassium, calcium, phosphorous, vitamins, other minerals, amino acids, fatty acids); or focussed on gastrointestinal development.

Co-primary outcomes were cognitive impairment (below −1 standard deviation [SD] on standard tests of cognitive development [toddlers] or cognition/intelligence quotient [later ages] or as defined by trialist) and any metabolic risk (any of the following defined by trialists: overweight/obese, increased waist circumference, increased fat mass or fat mass percentage, elevated plasma triglyceride concentrations, low high-density lipoprotein [HDL] concentrations, elevated low-density lipoprotein [LDL] concentrations, elevated fasting plasma glucose concentrations, insulin resistance, impaired glucose tolerance, diagnosis of type 2 diabetes, high blood pressure, impaired flow-mediated vasodilatation) (full list of outcomes in S1 Appendix). The outcomes were evaluated in toddlers (<3 years), childhood (3 to 8 years), and adolescence (9 to 18 years).

Data collection and analysis

Two reviewers (LL and EA) independently screened titles and abstracts of all records identified, assessed potentially eligible full-text articles for inclusion, extracted data into a template data extraction form, and assessed the risk of bias for included studies using Cochrane criteria [19]. Discrepancies were resolved by discussion or with a third author (JH).

We assessed risk of bias for each key outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [20] approach and created a "Summary of findings" table using the GradePro Guideline Development Tool (GDT; https://gradepro.org/). If a trial reported the same outcomes measured at different time points in childhood or beyond (>3 years), we chose the age group with the most data for assessment of the quality of evidence. We assessed quality of evidence for developmental outcomes for the following: composite of survival free of disability, cerebral palsy in toddlers, cognitive impairment in toddlers, cognitive scores in toddlers, motor impairment in toddlers, motor development scores in toddlers, and school performance. We assessed quality of evidence for metabolic outcomes for the following: overweight/obesity, triglyceride concentrations, HDL concentrations, LDL concentrations, systolic blood pressure (SBP), elevated fasting plasma glucose concentrations, and insulin resistance (all at >3 years).

Statistical analysis

We undertook meta-analyses using RevMan 5.3 [21] using random-effects models and calculated relative risks (RRs) and mean differences (MDs) with 95% confidence intervals [CIs]. $P < 0.05$ denoted statistical significance for all models, and this critical value was not split for each of the co-primary outcomes. We calculated I^2 and χ^2 tests to determine statistical heterogeneity, with $I^2 > 50\%$ and $P < 0.10$ considered significant heterogeneity. We assessed potential bias due to small study effects by visual inspection of funnel plots when there were more than 10 trials. We planned to conduct sensitivity analyses for GRADE outcomes by examining only trials considered to have low risk of selection and detection bias. We conducted subgroup analyses to explore whether the effects of supplements differed with sex, SGA, or timing of supplementation and tested for interactions for GRADE outcomes. No unplanned analyses were performed.

Results

After de-duplication, 7,288 records were identified. After title and abstract screening, we completed full-text screening for 271 records. We excluded 193 records that did not meet our inclusion criteria. We included the remaining 21 RCTs and 1 quasi-RCT with 3,680 infants in the qualitative analysis and 19 RCTs with 3,172 infants in the quantitative analysis (Fig 1). The included infants were born between 1963 and 2017. One study included term SGA infants [22], and the remaining 21 studies included preterm infants. Supplements were given in hospital in 10 studies [6,16,23–30], post discharge in 10 studies [31–40], and both in hospital and post discharge in 2 studies [22,41] (Table 1).

Risk of bias in included studies

Included studies were of variable methodological quality (S1A and S1B Fig), with 70% having a high risk of attribution bias due to loss to follow-up and 25% at high risk of performance bias because of lack of blinding [6,16,28,30,34]. The high risk of other bias in several studies was because of imbalance of baseline characteristics [22,24,34,36] and different baseline characteristics in each publication [33]. Nearly 30% were at unclear risk of other bias, particularly those

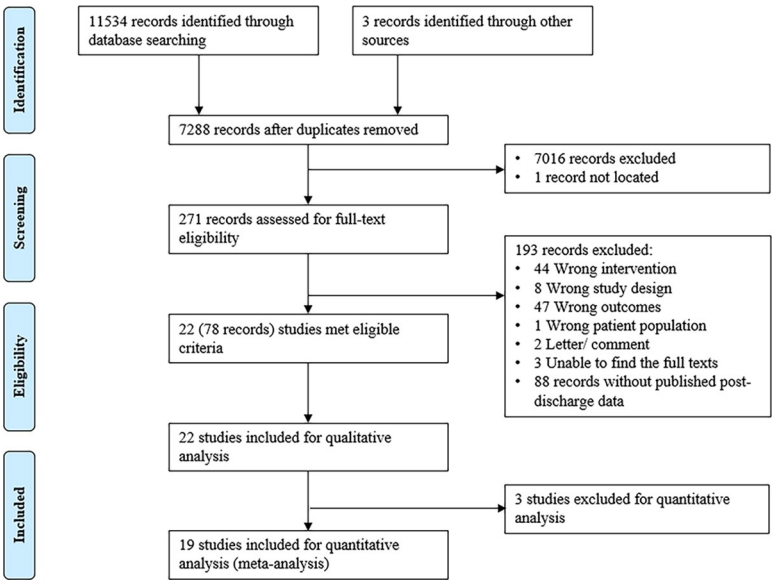

Fig 1. Flow diagram for included studies.

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Table 1. Characteristics of included studies.

Author/Year	Country	Participants	Participants, *n*	Intervention	Control	Duration	Outcomes
Agosti 2003 [31]	Italy	Inclusion criteria: preterm BW < 1,500 g and previously fed with a preterm formula Exclusion criteria: malformations intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, necrotizing enterocolitis grade >1, total parenteral nutrition >2 weeks, sepsis, retinopathy of prematurity grade >1	Intervention: 69 Control: 52	Preterm formula (protein 2.4 g/100 ml, energy 80 kcal/100 ml)	Standard term formula (protein 1.7 g/100 ml, energy 70 kcal/100 ml)	Started from 40 weeks PMA, stopped at 55 weeks PMA	GMDS at 6, 9, and 12 months' CA (Data presented in figures, no SD reported).
Amesz 2010 [32]	The Netherlands	Inclusion criteria: preterm GA ≤ 32 weeks or BW ≤ 1,500 g Exclusion criteria: congenital malformations or conditions known to affect growth or body composition (e.g., severe bronchopulmonary dysplasia, an inborn error of metabolism, cardiac or renal disease, necrotizing enterocolitis with substantial gut loss, grade 4 intraventricular hemorrhage)	Intervention: 52 Control: 50	Postdischarge formula (protein 1.7 g/100 ml, fat 3.5 g/100 ml, carbohydrate 7.0 g/100 ml, energy 67 kcal/100 ml)	Term formula (protein 1.47 g/100 ml, fat 3.5 g/100 ml, carbohydrate 7.2 g/100 ml, energy 70 kcal/100 ml)	Started from term, stopped at 6 months' CA	Blood pressure, triglycerides, HDL, LDL, fasting blood glucose concentration, insulin sensitivity, insulin resistance (HOMA-IR), fasting leptin at 8 years' CA.
Bellagamba 2016 [23]	Italy	Inclusion criteria: preterm BW between 500 and 1,249 g	Intervention: 82 Control: 82	High protein intake group (protein supplementation started at 1.5 g/kg/day and increased by 0.5 g/kg/day to a maximum of 3.5 g/kg/day on the fifth day after birth)	Standard protein intake group (protein supplementation started at 1.5g/kg/day and increased by 0.5 g/kg/day to a maximum of 2.5 g/kg/day on the third day after birth)	Started from birth, stopped at discharge	Bayley III at 2 years' CA.
Biasini 2012 [24]	Italy	Inclusion criteria: preterm BW between 580 and 1,250 g and GA < 32 weeks	Intervention: 34 Control: 27	Protein supplemented group (protein 4.8 g/kg/day, energy 141 kcal/day)	Control group (protein 3.5 g/kg/day, energy 135 kcal/day)	Started from the first day of full enteral feeding, stopped at discharge	GMDS at 12 and 18 months' CA; GMDS at 18 and 24 months' CA for SGA infants.
Cooke 2001 [33]	UK	Inclusion criteria: preterm GA ≤ 34 weeks and BW ≤ 1,750 g, and growing normally at the time of hospital discharge, i.e., ≥25 g/d Exclusion criteria: systemic disease or require medication	Intervention: 56 Control: 57	Preterm formula (protein 2.2 g/100 ml, fat 4.4 g/100 ml, carbohydrate 8.5 g/100 ml, energy 80 kcal/100 ml)	Term formula (protein 1.4 g/100 ml, fat 3.6 g/100 ml, carbohydrate 7.5 g/100 ml, energy 66 kcal/100 ml)	Started from discharge, stopped at 6 months' CA	Bayley II at 18 months' CA.

(*Continued*)

Table 1. (Continued)

Author/Year	Country	Participants	Participants, *n*	Intervention	Control	Duration	Outcomes
Cooper 1988 [25]	South Africa	Inclusion criteria: preterm GA < 36 weeks and BW < 1,600 g Exclusion criteria: major congenital abnormalities, congenital infections or severe intrauterine growth retardation, or withdrawn from the study (if intake of own mother's milk was > 100 kcal/kg/d)	Intervention: 10 Control: 10	Preterm formula (protein 2.2 g/100 ml, fat 3.66 g/100 ml, carbohydrate 8.6 g/100 ml, energy 75 kcal/100 ml)	Standard formula (protein 1.6 g/100 ml, fat 3.4 g/100 ml, carbohydrate 7.4 g/100 ml, energy 67 kcal/100 ml)	Started from the day that half the caloric intake was enteral and stopped after 5 weeks or when infants reached 2,000 g	GMDS at 12 months' and 3 years' CA.
da Cunha 2016 [34]	Brazil	Inclusion criteria: preterm GA < 37 weeks and BW < 1,500 g, and discharged exclusively breastfeeding Exclusion criteria: major malformations; hydrocephalus; chromosomal abnormalities; fetal hydrops; congenital infections; maternal use of illicit drugs, tobacco, alcohol, and continuous use of corticosteroids; twin pregnancy; necrotizing enterocolitis sequelae; cerebral palsy	Intervention: 27 Control: 27	Breast milk supplementation (daily increase of 0.56 g of protein, 1.04 g of total fat, and 2.12 g of carbohydrates)	Breast milk without supplementation	Started 7–10 days after discharge, stopped at 4 to 6 months	Bayley III at 12 months' CA
Dogra 2017 [26]	India	Inclusion criteria: preterm GA < 32 weeks Exclusion criteria: lethal congenital malformations	Intervention: 59 Control: 56	Fortified breast milk with higher enteral protein intake (fortifier containing protein 1.0 g/100 mL, fat 0.01 g/ 100 mL, carbohydrate 3.6 g/100 mL, energy 17.2 kcal/100 mL)	Fortified breast milk with standard enteral protein intake (fortifier containing protein 0.4 g/100 mL, fat 0.2 g/100 mL, carbohydrate 2.4 g/100 mL, energy 13 kcal/100 mL)	Started when infants reached a feed volume of 100 mL/kg/ day, stopped at discharge or full breastfeeds, whichever was earlier	DASII at 12 to 18 months' CA
Fewtrell 2001 [22]	UK	Inclusion criteria: GA ≥ 37 weeks and BW below the 10th centile for gestation and sex according to UK growth charts	Intervention: 152 Control: 147	Enriched formula (protein 1.85 g/100 mL, fat 3.96 g/100 mL, carbohydrate 7.24 g/ 100 mL, energy 72 kcal/100 mL)	Term formula (protein 1.45 g/100 mL, fat 3.85 g/100 mL, carbohydrate 6.96 g/ 100 mL, energy 68 kcal/100 mL)	Started within the first week, stopped at 9 months' CA	Bayley II at 9 and 18 months' CA; blood pressure at 6 to 8 years' CA
Friel 1993 [35]	Canada	Inclusion criteria: BW < 1,500 g Exclusion criteria: breast-fed, hydrocephalus, liver dysfunction, or any congenital malformations	Intervention: 27 Control: 27	Low BW formula (protein 1.73 g/100 mL, fat 3.7 g/100 mL, carbohydrate 7.1 g/100 mL, energy 67 kcal/100 mL)	Term formula (protein 1.57 g/100 mL, fat 3.6 g/100 mL, carbohydrate 7.3 g/100 mL, energy 67 kcal/100 mL)	Started when the infants reached a weight of 1,850 ± 100 g, stopped at 5 months after discharge	GMDS at 3, 6, 9, 12 months' CA (Data presented in figures, no SD reported).

(*Continued*)

Table 1. (Continued)

Author/Year	Country	Participants	Participants, *n*	Intervention	Control	Duration	Outcomes
Goldman 1969 [27]	US	Inclusion criteria: BW < 2,000 g Exclusion criteria: major congenital malformations, intestinal obstruction, Rhesus disease, >3 days old on admission, or died during the first few days generally received no milk feedings	Intervention: 152 Control: 152	Enriched formula (protein 4.0 g/100 mL, fat 3.9 g/100 mL, carbohydrate 7.6 g/10 mml, 80 kcal/100 mL)	Standard formula (protein 2.0 g/100 mL, fat 3.9 g/100 mL, carbohydrate 9.6 g/100 mL, energy 80 kcal/100 mL)	Started from 24 to 72 hours, stopped when the infants reached 2,200 g (at discharge)	Cognitive impairment (Stanford-Binet scores) at 3 years' CA.
Jeon 2011 [36]	Korea	Inclusion criteria: preterm GA < 33 weeks and BW < 1,500 g, formula as the primary food source Exclusion criteria: chromosomal disorders or serious congenital malformations at discharge that would affect growth and development	Intervention: 35 Control: 34	Preterm formula (protein 2.3 g/100 mL, fat 4.1 g/100 mL, carbohydrate 8.5 g/100 mL, energy 80 kcal/100 mL)	Term formula (protein 1.6 g/100 mL, fat 3.5 g/100 mL, carbohydrate 7.2 g/100 mL, energy 67 kcal/100 mL)	Started at term, stopped at 6 months' CA	Bayley II at 18 months' CA.
Lucas 1989 [28]	UK	Inclusion criteria: preterm GA < 37 weeks and BW < 1,850 g Exclusion criteria: major congenital abnormality known to impair growth or development, or died before randomization within the first 48 hours	(1) Lucas 1989a: Intervention: 76 Control: 83 (2) Lucas 1989b: Intervention: 173 Control: 170 (3) Lucas 1989c: combined Lucas 1989a and Lucas 1989b: Intervention: 249 Control: 253	(1) Lucas 1989a Preterm formula as sole diet (protein 2.0 g/100 mL, fat 4.9 g/100 mL, carbohydrate 7.0 g/100 mL, energy 80 kcal/100 mL) (2) Lucas 1989b Preterm formula as supplement (3) Lucas 1989c: combined Lucas 1989a and Lucas 1989b	(1) Lucas 1989a: Banked breast milk as sole diet (protein 1.1 g/100 mL, fat 1.7 g/100 mL, carbohydrate 7.1 g/100 mL, energy 46 kcal/100 mL) (2) Lucas 1989b: banked breast milk as supplement (3) Lucas 1989c: combined Lucas 1989a and Lucas 1989b	Started within 48 hours, stopped at discharge or when the infants reached 2,000 g	Bayley II at 9, 18 months' CA; Blood pressure at 7.5 to 8 years' and 13 to 16 years' CA; Triglycerides, HDL, LDL, fasting blood glucose concentration, fasting insulin concentration, insulin resistance (fasting 32–33 split proinsulin) at 13 to 16 years' CA.
Lucas 1990 [16]	UK	Inclusion criteria: preterm BW < 1,850 g and GA < 37 weeks Exclusion criteria: major congenital abnormality known to impair growth or development or died before randomization within the first 48 hours	(1) Lucas 1990a: Intervention: 81 Control: 79 (2) Lucas 1990b: Intervention: 132 Control: 132 (3) Lucas 1990c: combined Lucas 1990a and Lucas 1990b: Intervention: 213 Control: 211	(1) Lucas 1990a: Preterm formula as sole diet (protein 2.0 g/100 mL, fat 4.9 g/100 mL, carbohydrate 7.0 g/100 mL, energy 80 kcal/100 mL) (2) Lucas 1990b Preterm formula as supplement (3) Lucas 1990c: combined Lucas 1990a and Lucas 1990b	(1) Lucas 1990a: term formula as sole diet (protein 1.5 g/100 mL, fat 3.8 g/100 mL, carbohydrate 7.0 g/100 mL, energy 68 kcal/100 mL) (2) Lucas 1990b: term formula as supplement (3) Lucas 1990c: combined Lucas 1990a and Lucas 1990b	Started within 48 hours, stopped at discharge or when the infants reached 2,000 g	Bayley II at 9, 18 months' CA; WISC at 7.5 to 8 years' CA; Blood pressure at 7.5 to 8 years' and 13 to 16 years' CA; Triglycerides, HDL, LDL, fasting blood glucose concentration, fasting insulin concentration, insulin resistance (fasting 32–33 split proinsulin) at 13 to 16 years' CA.

(*Continued*)

Table 1. (Continued)

Author/Year	Country	Participants	Participants, *n*	Intervention	Control	Duration	Outcomes
Lucas 1996 [6]	UK	Inclusion criteria: preterm BW < 1,850 g, GA < 37 weeks, and survived to be assigned to a study group between 48 and 72 hours of age Exclusion criteria: major congenital anomalies	Intervention: 137 Control: 138	Fortified human breast milk; fortifier containing protein 0.7 g/100 mL, fat 0.05 g/100 mL, carbohydrate 2.73 g/100 mL, energy 14 kcal/100 mL	Human breast milk	Started within 48 hours, stopped at discharge or when the infants reached 2,000 g	Bayley II at 9, 18 months' CA.
Lucas 2001 [37]	UK	Inclusion criteria: preterm GA < 37 weeks and BW < 1,750 g Exclusion criteria: congenital malformations or conditions known to affect growth or development	Intervention: 113 Control: 116	Postdischarge formula (protein 1.85 g/100 mL, fat 3.96 g/100 mL, carbohydrate 7.24 g/100 mL, energy 72 kcal/100 mL)	Term formula (protein 1.45 g/100 mL, fat 3.82 g/100 mL carbohydrate 6.96 g/100 mL, energy 68 kcal/100 mL)	Started one week before discharge, stopped at 9 months post term	Bayley II at 18 months' CA.
Morgan 2014 [29]	UK	Inclusion criteria: preterm GA between 24 to 28 weeks and BW < 1,200 g Exclusion criteria: unlikely to survive the first week after birth; diagnosed with major congenital or chromosomal abnormalities known to affect gastrointestinal function or head growth, including definite parenchymal lesions on cranial ultrasound scan in first 48 hours	Intervention: 74 Control: 76	Standard macronutrient content (parenteral intake with protein 3.8 g/kg/day, fat 3.8 g/kg/day, carbohydrate 15.6 g/kg/day, energy 103 kcal/kg/day)	Higher macronutrient content (parenteral intake with protein 2.8 g/kg/day, fat 2.8 g/kg/day, carbohydrate 13.5 g/kg/day, energy 85 kcal/kg/day)	Started within 120 hours of birth, stopped at 28 days	Bayley III at 2 to 3.5 years of CA.
O'Connor 2008 [38]	Canada	Inclusion criteria: preterm GA < 33 weeks and BW between 750 and 1,800 g who received ≥80% of their total feedings as human milk 3 days before hospital discharge Exclusion criteria: serious congenital or chromosomal anomalies that could affect growth, grade 3 or 4 periventricular or intraventricular hemorrhage, oral steroids within 14 days of randomization, severe asphyxia, and known maternal alcohol or drug abuse	Intervention: 19 Control: 20	Human milk with a multinutrient fortifier (protein 2.0 g/100 mL, fat 4.2 g/100 mL, carbohydrate 8.8 g/100 mL, energy 81 kcal/100 mL)	Unfortified human milk (protein 1.3 g/100 mL, fat 3.9 g/100 mL, carbohydrate 7.2 g/100 mL, energy 68 kcal/100 mL)	Started from discharge, stopped at 12 weeks after discharge	Bayley II at 18 months' CA.

(*Continued*)

Table 1. (Continued)

Author/Year	Country	Participants	Participants, *n*	Intervention	Control	Duration	Outcomes
Roggero 2012 [39]	Italy	Inclusion criteria: preterm GA ≤ 32 weeks or BW ≤ 1,500 g and being fed human milk for 20% of the total milk intake Exclusion criteria: congenital malformations or conditions that interfere with growth or body composition	Intervention: 110 Control: 107	Nutrient-enriched formula (protein 2.0 g/100 mL, fat 4.1 g/100 mL, carbohydrate 7.5 g/100 mL, energy 75 kcal/100 mL)	Term formula (protein 1.4 g/100 mL, fat 3.7 g/100 mL, carbohydrate 7.4 g/100 mL, energy 68 kcal/100 mL)	Started from term CA, stopped at 6 months	GMDS at 24 months' CA.
Svenningsen 1982 [41]	Sweden	Inclusion criteria: Very low BW preterm with mean BW 1,385 ± 343 g and GA 30.8 ± 2.9 weeks	Intervention: 16 Control: 14	Nutrition enriched formula (protein 2.1 g/100 mL, energy 69.5 kcal/100 mL)	Standard formula (protein 1.6 g/100 mL, energy 68.5 kcal/100 mL)	Started from the third week after birth, stopped at the seventh week after birth	Development impairments at 6 months, 1 and 2 years of age.
Tan 2008 [30]	UK	Inclusion criteria: preterm GA < 29 weeks Exclusion criteria: triplets and higher multiplicity, admitted after 7 days of age, major congenital abnormalities	Intervention: 68 Control: 74	Parenteral intake with protein 4 g/kg/day, fat 4 g/kg/day, carbohydrate 16.3 g/kg/day, energy 117 kcal/kg/day; enteral intake breast milk or formula with target protein 4 g/kg/day, energy 133–150 kcal/kg/day	Parenteral intake with protein 3 g/kg/day, fat 3 g/kg/day, carbohydrate 13.5 g/kg/day, energy 93 kcal/kg/day; enteral intake breast milk or formula with target protein 3.3 g/kg/day, energy 133 kcal/kg/day	Started when infants received parenteral and enteral nutrition from the first week, stopped at 34 weeks' PMA	Bayley II at 3 and 9 months' CA.
Zachariassen 2001 [40]	Denmark	Inclusion criteria: preterm GA ≤ 32 weeks, breastfeeding Exclusion criteria: severe diseases or circumstances influencing eating and feeding ability at discharge	Intervention: 105 Control: 102	Fortified mother's milk (protein 1.375 g/day, energy 17.5 kcal/day)	Unfortified mother's milk	Started from shortly before discharge, stopped at 4 months' CA	Obesity, type 2 diabetes, high blood pressure, blood pressure, triglycerides, HDL, LDL, fasting blood glucose concentration, fasting insulin concentration, at 6 years' CA.

GMDS measures locomotor skills, personal-social, hearing, language, eye and hand coordination, performance, and practical reasoning. DASI I measures mental and motor development. Bayley-II measures mental and psychomotor development. Bayley-III measures cognitive, motor and language development. The Stanford-Binet test measures cognitive development, including fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory.

Abbreviations: Bayley-II, Bayley Scales of Infant and Toddler Development-Edition II; Bayley-III, Bayley Scales of Infant and Toddler Development-Edition III; BW, birth weight; CA, corrected age; DASII, Developmental Assessment Scales for Indian Infants-Edition II; GA, gestational age; GMDS, Griffith Mental Developmental Scale; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; PMA, post-menstrual age; SD, standard deviation; WISC, Wechsler Intelligence Scale for Children

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supported by formula or fortifier companies where the role of the funders was not clear [6,16,22,27,28,32,33,37]. One study [25] was at high risk of selection bias because the infants were randomised according to the last digit of the infants' hospital number.

Co-primary outcome: Cognitive impairment and metabolic risk

There was no difference between supplemented and unsupplemented groups in cognitive impairment in toddlers (5 trials [16,27,29,34,36]; 719 children; RR 1.00; 95% CI 0.67–1.49; $P = 0.99$; Fig 2A) or in childhood (2 trials [16,27]; 370 children; RR 0.81; 95% CI 0.26–2.57; $P = 0.72$; Fig 2A).

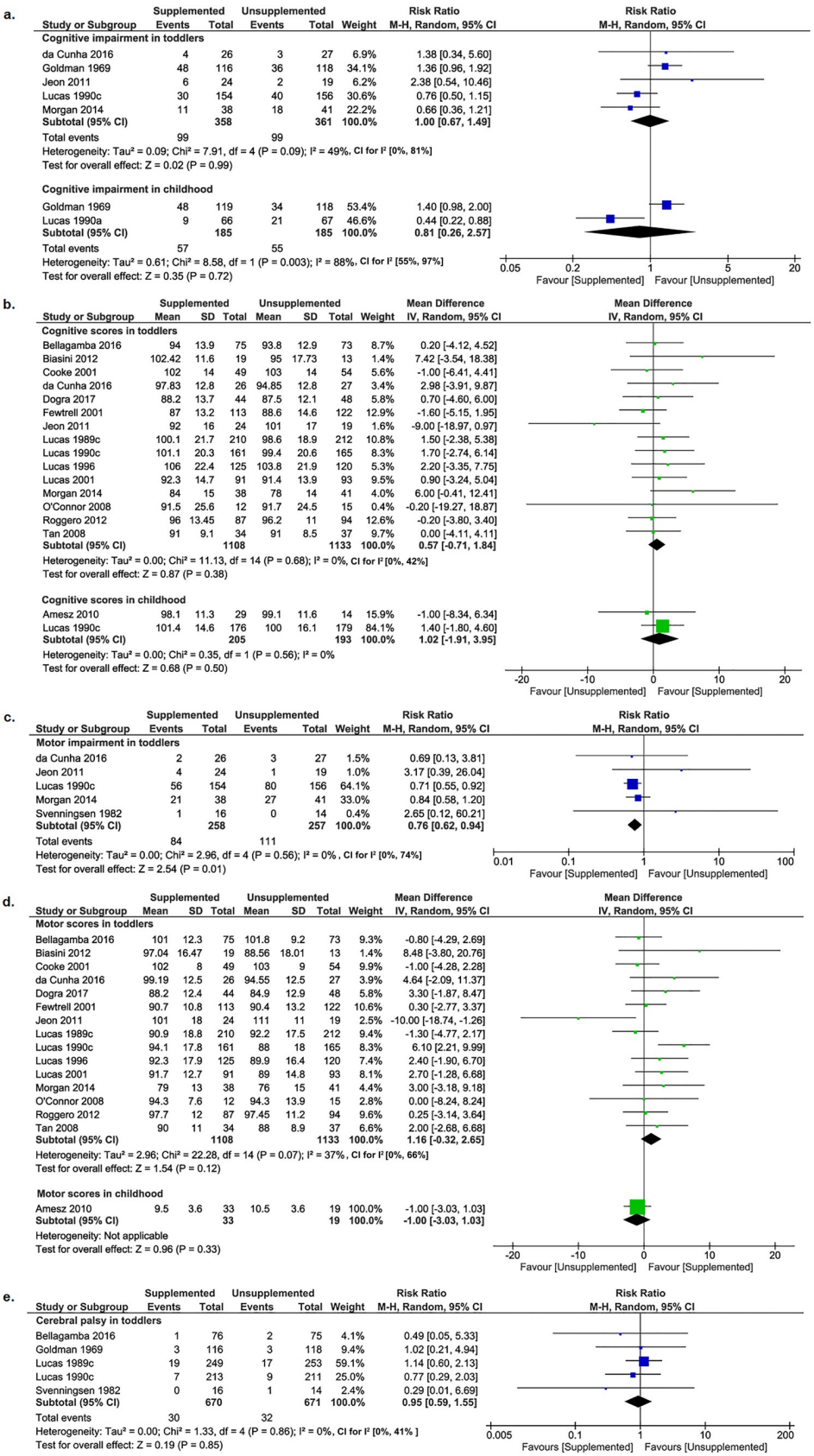
a.
Supplemented
Unsupplemented
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Cognitive impairment in toddlers
da Cunha 2016 4 26 3 27 6.9% 1.38 [0.34, 5.60]
Goldman 1969 48 116 36 118 34.1% 1.36 [0.96, 1.92]
Jeon 2011 6 24 2 19 6.2% 2.38 [0.54, 10.46]
Lucas 1990c 30 154 40 156 30.6% 0.76 [0.50, 1.15]
Morgan 2014 11 38 18 41 22.2% 0.66 [0.36, 1.21]
Subtotal (95% CI) 358 361 100.0% 1.00 [0.67, 1.49]
Total events 99 99
Heterogeneity: Tau² = 0.09; Chi² = 7.91, df = 4 (P = 0.09); I² = 49%, CI for I² [0%, 81%]
Test for overall effect: Z = 0.02 (P = 0.99)
Cognitive impairment in childhood
Goldman 1969 48 119 34 118 53.4% 1.40 [0.98, 2.00]
Lucas 1990a 9 66 21 67 46.6% 0.44 [0.22, 0.88]
Subtotal (95% CI) 185 185 100.0% 0.81 [0.26, 2.57]
Total events 57 55
Heterogeneity: Tau² = 0.61; Chi² = 8.58, df = 1 (P = 0.003); I² = 88%, CI for I² [55%, 97%]
Test for overall effect: Z = 0.35 (P = 0.72)
0.05 0.2 1 5 20
Favour [Supplemented] Favour [Unsupplemented]
b.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Cognitive scores in toddlers
Bellagamba 2016 94 13.9 75 93.8 12.9 73 8.7% 0.20 [-4.12, 4.52]
Biasini 2012 102.42 11.6 19 95 17.73 13 1.4% 7.42 [-3.54, 18.38]
Cooke 2001 102 14 49 103 14 54 5.6% -1.00 [-6.41, 4.41]
da Cunha 2016 97.83 12.8 26 94.85 12.8 27 3.4% 2.98 [-3.91, 9.87]
Dogra 2017 88.2 13.7 44 87.5 12.1 48 5.8% 0.70 [-4.60, 6.00]
Fewtrell 2001 87 13.2 113 88.6 14.6 122 12.9% -1.60 [-5.15, 1.95]
Jeon 2011 92 16 24 101 17 19 1.6% -9.00 [-18.97, 0.97]
Lucas 1989c 100.1 21.7 210 98.6 18.9 212 10.8% 1.50 [-2.38, 5.38]
Lucas 1990c 101.1 20.3 161 99.4 20.6 165 8.3% 1.70 [-2.74, 6.14]
Lucas 1996 106 22.4 125 103.8 21.9 120 5.3% 2.20 [-3.35, 7.75]
Lucas 2001 92.3 14.7 91 91.4 13.9 93 9.5% 0.90 [-3.24, 5.04]
Morgan 2014 84 15 38 78 14 41 4.0% 6.00 [-0.41, 12.41]
O'Connor 2008 91.5 25.6 12 91.7 24.5 15 0.4% -0.20 [-19.27, 18.87]
Roggero 2012 96 13.45 87 96.2 11 94 12.6% -0.20 [-3.80, 3.40]
Tan 2008 91 9.1 34 91 8.5 37 9.7% 0.00 [-4.11, 4.11]
Subtotal (95% CI) 1108 1133 100.0% 0.57 [-0.71, 1.84]
Heterogeneity: Tau² = 0.00; Chi² = 11.13, df = 14 (P = 0.68); I² = 0%, CI for I² [0%, 42%]
Test for overall effect: Z = 0.87 (P = 0.38)
Cognitive scores in childhood
Amesz 2010 98.1 11.3 29 99.1 11.6 14 15.9% -1.00 [-8.34, 6.34]
Lucas 1990c 101.4 14.6 176 100 16.1 179 84.1% 1.40 [-1.80, 4.60]
Subtotal (95% CI) 205 193 100.0% 1.02 [-1.91, 3.95]
Heterogeneity: Tau² = 0.00; Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.68 (P = 0.50)
-20 -10 0 10 20
Favour [Unsupplemented] Favour [Supplemented]
c.
Supplemented
Unsupplemented
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Motor impairment in toddlers
da Cunha 2016 2 26 3 27 1.5% 0.69 [0.13, 3.81]
Jeon 2011 4 24 1 19 1.0% 3.17 [0.39, 26.04]
Lucas 1990c 56 154 80 156 64.1% 0.71 [0.55, 0.92]
Morgan 2014 21 38 27 41 33.0% 0.84 [0.58, 1.20]
Svenningsen 1982 1 16 0 14 0.4% 2.65 [0.12, 60.21]
Subtotal (95% CI) 258 257 100.0% 0.76 [0.62, 0.94]
Total events 84 111
Heterogeneity: Tau² = 0.00; Chi² = 2.96, df = 4 (P = 0.56); I² = 0% , CI for I² [0%, 74%]
Test for overall effect: Z = 2.54 (P = 0.01)
0.01 0.1 1 10 100
Favour [Supplemented] Favour [Unsupplemented]
d.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Motor scores in toddlers
Bellagamba 2016 101 12.3 75 101.8 9.2 73 9.3% -0.80 [-4.29, 2.69]
Biasini 2012 97.04 16.47 19 88.56 18.01 13 1.4% 8.48 [-3.80, 20.76]
Cooke 2001 102 8 49 103 9 54 9.9% -1.00 [-4.28, 2.28]
da Cunha 2016 99.19 12.5 26 94.55 12.5 27 3.9% 4.64 [-2.09, 11.37]
Dogra 2017 88.2 12.4 44 84.9 12.9 48 5.8% 3.30 [-1.87, 8.47]
Fewtrell 2001 90.7 10.8 113 90.4 13.2 122 10.6% 0.30 [-2.77, 3.37]
Jeon 2011 101 18 24 111 11 19 2.5% -10.00 [-18.74, -1.26]
Lucas 1989c 90.9 18.8 210 92.2 17.5 212 9.4% -1.30 [-4.77, 2.17]
Lucas 1990c 94.1 17.8 161 88 18 165 8.3% 6.10 [2.21, 9.99]
Lucas 1996 92.3 17.9 125 89.9 16.4 120 7.4% 2.40 [-1.90, 6.70]
Lucas 2001 91.7 12.7 91 89 14.8 93 8.1% 2.70 [-1.28, 6.68]
Morgan 2014 79 13 38 76 15 41 4.4% 3.00 [-3.18, 9.18]
O'Connor 2008 94.3 7.6 12 94.3 13.9 15 2.8% 0.00 [-8.24, 8.24]
Roggero 2012 97.7 12 87 97.45 11.2 94 9.6% 0.25 [-3.14, 3.64]
Tan 2008 90 11 34 88 8.9 37 6.6% 2.00 [-2.68, 6.68]
Subtotal (95% CI) 1108 1133 100.0% 1.16 [-0.32, 2.65]
Heterogeneity: Tau² = 2.96; Chi² = 22.28, df = 14 (P = 0.07); I² = 37% , CI for I² [0%, 66%]
Test for overall effect: Z = 1.54 (P = 0.12)
Motor scores in childhood
Amesz 2010 9.5 3.6 33 10.5 3.6 19 100.0% -1.00 [-3.03, 1.03]
Subtotal (95% CI) 33 19 100.0% -1.00 [-3.03, 1.03]
Heterogeneity: Not applicable
Test for overall effect: Z = 0.96 (P = 0.33)
-20 -10 0 10 20
Favour [Unsupplemented] Favour [Supplemented]
e.
Supplemented
Unsupplemented
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Cerebral palsy in toddlers
Bellagamba 2016 1 76 2 75 4.1% 0.49 [0.05, 5.33]
Goldman 1969 3 116 3 118 9.4% 1.02 [0.21, 4.94]
Lucas 1989c 19 249 17 253 59.1% 1.14 [0.60, 2.13]
Lucas 1990c 7 213 9 211 25.0% 0.77 [0.29, 2.03]
Svenningsen 1982 0 16 1 14 2.4% 0.29 [0.01, 6.69]
Subtotal (95% CI) 670 671 100.0% 0.95 [0.59, 1.55]
Total events 30 32
Heterogeneity: Tau² = 0.00; Chi² = 1.33, df = 4 (P = 0.86); I² = 0%, CI for I² [0%, 41%]
Test for overall effect: Z = 0.19 (P = 0.85)
0.005 0.1 1 10 200
Favours [Supplemented] Favours [Unsupplemented]

Fig 2. Forest plots of effect of macronutrient supplementation on primary and secondary developmental outcomes. (a) Cognitive impairment (primary outcome); (b) cognitive scores; (c) motor impairment; (d) motor scores; (e) cerebral palsy (all secondary outcomes). Blue boxes in the forest plots represent the dichotomous data; green boxes represent the continuous data. CI, confidence interval; M-H, Mantel-Haenszel; IV, inverse variance.

https://doi.org/10.1371/journal.pmed.1002952.g002

One trial [40] reported the incidence of obesity, high blood pressure, and type 2 diabetes in childhood, but it was not possible to extract data about the number of individual children who experienced any of these outcomes.

Secondary developmental outcomes

There was no difference between supplemented and unsupplemented groups in cognitive scores in toddlers (15 trials [6,16,22–24,26,28–30,33,34,36–39]; 2,241 children; MD 0.57; 95% CI −0.71 to 1.84; $P = 0.38$; Fig 2B) or in childhood (2 trials [16,32]; 398 children; MD 1.02; 95% CI −1.91 to 3.95; $P = 0.50$; Fig 2B). Sensitivity analysis including only studies at low risk of bias did not alter the findings of cognitive scores in toddlers (6 trials [16,22,26,28–30]; 1,225 children; MD 0.73; 95% CI −1.05 to 2.51; $P = 0.42$; S2A Fig), and funnel plots (S3A Fig) did not suggest significant bias due to small study effects.

Toddlers in the supplemented group had a lower risk of motor impairment than the unsupplemented group (5 trials [16,29,34,36,41]; 515 children; RR 0.76; 95% CI 0.62 to 0.94; $P = 0.01$; Fig 2C). There was no difference between supplemented and unsupplemented groups in motor scores in toddlers (15 trials [6,16,22–24,26,28–30,33,34,36–39]; 2,241 children; MD 1.16; 95% CI −0.32 to 2.65; $P = 0.12$; Fig 2D) or in childhood (1 trial [32]; 52 children; MD −1.00; 95% CI −3.03 to 1.03; $P = 0.33$; Fig 2D). Sensitivity analysis including only studies at low risk of bias did not alter the findings of motor scores in toddlers (6 trials [16,22,26,28–30], 1,225 children, MD 1.96; 95% CI −0.36 to 4.28; $P = 0.10$; S2B Fig), and funnel plots (S3B Fig) did not suggest significant bias due to small study effects.

There was no clear difference in the incidence of cerebral palsy in toddlers between supplemented and unsupplemented groups (5 trials [16,23,27,28,41]; 1,341 children; RR 0.95; 95% CI 0.59 to 1.55; $P = 0.85$; Fig 2E).

One trial [27] (234 children) reported visual and hearing impairment in toddlers. There was no difference between supplemented and unsupplemented groups in visual impairment (RR 1.02; 95% CI 0.06 to 16.07; $P = 0.99$; S4A Fig) or hearing impairment (RR 0.20; 95% CI 0.01 to 4.19; $P = 0.30$; S4B Fig).

Secondary metabolic outcomes

One trial (150 children) [40] found no differences between supplemented and unsupplemented groups in childhood for type 2 diabetes (RR 2.25; 95% CI 0.45–11.22; $P = 0.32$), obesity (RR 0.75; 95% CI 0.34–1.63; $P = 0.47$), and high blood pressure (RR 2.47; 95% CI 0.82–7.41; $P = 0.11$; Fig 3A).

There were no differences between supplemented and unsupplemented groups in triglyceride concentrations in childhood (2 trials [32,40]; 189 children; MD −0.11 mmol/L; 95% CI −0.57 to 0.35 mmol/L; $P = 0.65$; Fig 3B) or in adolescence (2 trials [16,28]; 202 children; MD 0.04 mmol/L; 95% CI −0.26 to 0.33 mmol/L; $P = 0.81$; Fig 3B) or at >3 years (4 trials [16,28,32,40]; 391 children; MD −0.04 mmol/L; 95% CI −0.31 to 0.24 mmol/L; $P = 0.79$; Fig 3B).

In childhood, supplemented children had higher HDL concentrations than unsupplemented children (2 trials [32,40]; 189 children; MD 0.11 mmol/L; 95% CI 0.02–0.19 mmol/L; $P = 0.02$; Fig 3C). In adolescence, there was no difference in HDL concentrations between

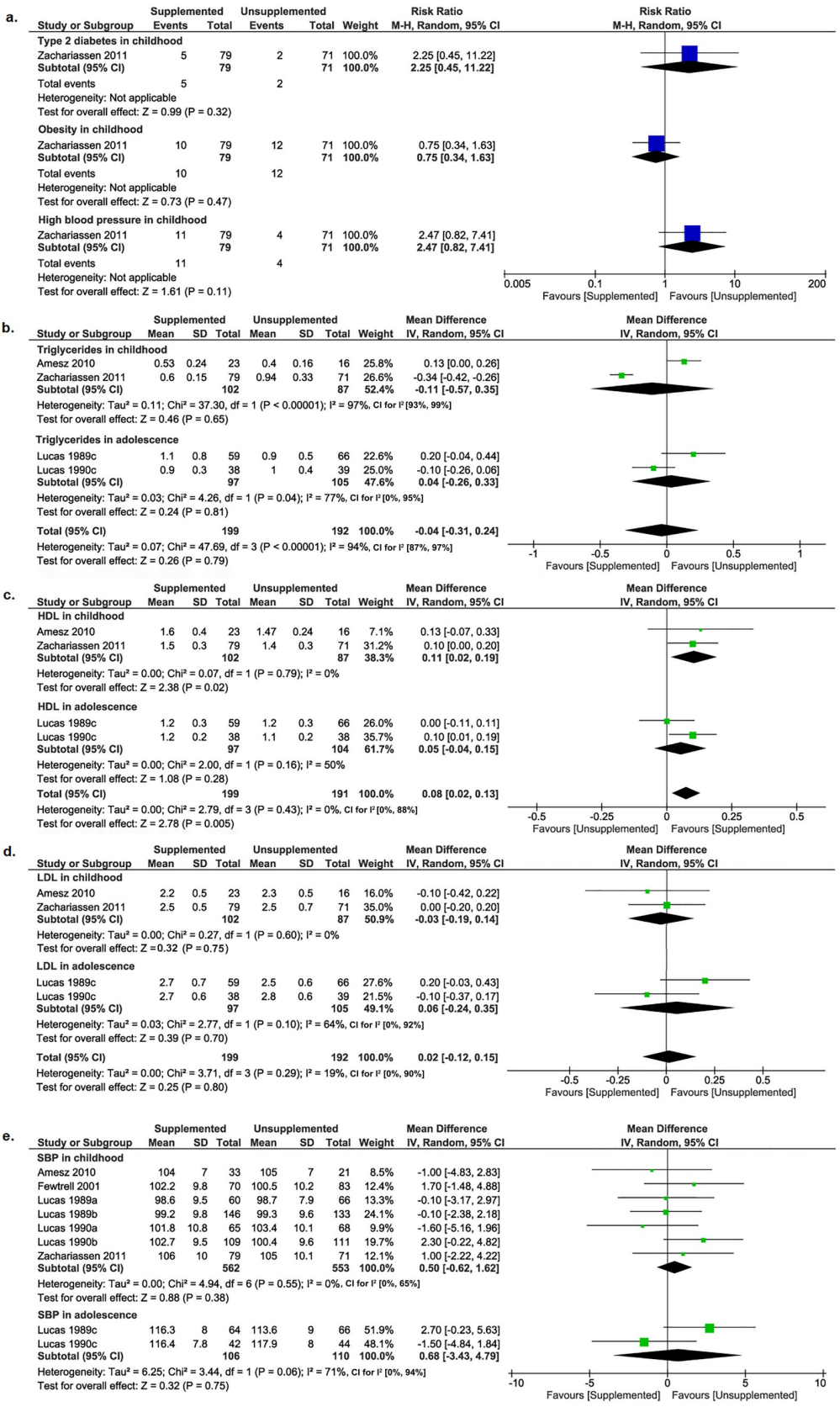
a.
Supplemented
Unsupplemented
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Type 2 diabetes in childhood
Zachariassen 2011 5 79 2 71 100.0% 2.25 [0.45, 11.22]
Subtotal (95% CI) 79 71 100.0% 2.25 [0.45, 11.22]
Total events 5 2
Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)
Obesity in childhood
Zachariassen 2011 10 79 12 71 100.0% 0.75 [0.34, 1.63]
Subtotal (95% CI) 79 71 100.0% 0.75 [0.34, 1.63]
Total events 10 12
Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.47)
High blood pressure in childhood
Zachariassen 2011 11 79 4 71 100.0% 2.47 [0.82, 7.41]
Subtotal (95% CI) 79 71 100.0% 2.47 [0.82, 7.41]
Total events 11 4
Heterogeneity: Not applicable
Test for overall effect: Z = 1.61 (P = 0.11)
0.005 0.1 1 10 200
Favours [Supplemented] Favours [Unsupplemented]
b.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Triglycerides in childhood
Amesz 2010 0.53 0.24 23 0.4 0.16 16 25.8% 0.13 [0.00, 0.26]
Zachariassen 2011 0.6 0.15 79 0.94 0.33 71 26.6% -0.34 [-0.42, -0.26]
Subtotal (95% CI) 102 87 52.4% -0.11 [-0.57, 0.35]
Heterogeneity: Tau² = 0.11; Chi² = 37.30, df = 1 (P < 0.00001); I² = 97%, CI for I² [93%, 99%]
Test for overall effect: Z = 0.46 (P = 0.65)
Triglycerides in adolescence
Lucas 1989c 1.1 0.8 59 0.9 0.5 66 22.6% 0.20 [-0.04, 0.44]
Lucas 1990c 0.9 0.3 38 1 0.4 39 25.0% -0.10 [-0.26, 0.06]
Subtotal (95% CI) 97 105 47.6% 0.04 [-0.26, 0.33]
Heterogeneity: Tau² = 0.03; Chi² = 4.26, df = 1 (P = 0.04); I² = 77%, CI for I² [0%, 95%]
Test for overall effect: Z = 0.24 (P = 0.81)
Total (95% CI) 199 192 100.0% -0.04 [-0.31, 0.24]
Heterogeneity: Tau² = 0.07; Chi² = 47.69, df = 3 (P < 0.00001); I² = 94%, CI for I² [87%, 97%]
Test for overall effect: Z = 0.26 (P = 0.79)
-1 -0.5 0 0.5 1
Favours [Supplemented] Favours [Unsupplemented]
c.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
HDL in childhood
Amesz 2010 1.6 0.4 23 1.47 0.24 16 7.1% 0.13 [-0.07, 0.33]
Zachariassen 2011 1.5 0.3 79 1.4 0.3 71 31.2% 0.10 [0.00, 0.20]
Subtotal (95% CI) 102 87 38.3% 0.11 [0.02, 0.19]
Heterogeneity: Tau² = 0.00; Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.38 (P = 0.02)
HDL in adolescence
Lucas 1989c 1.2 0.3 59 1.2 0.3 66 26.0% 0.00 [-0.11, 0.11]
Lucas 1990c 1.2 0.2 38 1.1 0.2 38 35.7% 0.10 [0.01, 0.19]
Subtotal (95% CI) 97 104 61.7% 0.05 [-0.04, 0.15]
Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 1 (P = 0.16); I² = 50%
Test for overall effect: Z = 1.08 (P = 0.28)
Total (95% CI) 199 191 100.0% 0.08 [0.02, 0.13]
Heterogeneity: Tau² = 0.00; Chi² = 2.79, df = 3 (P = 0.43); I² = 0%, CI for I² [0%, 88%]
Test for overall effect: Z = 2.78 (P = 0.005)
-0.5 -0.25 0 0.25 0.5
Favours [Unsupplemented] Favours [Supplemented]
d.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
LDL in childhood
Amesz 2010 2.2 0.5 23 2.3 0.5 16 16.0% -0.10 [-0.42, 0.22]
Zachariassen 2011 2.5 0.5 79 2.5 0.7 71 35.0% 0.00 [-0.20, 0.20]
Subtotal (95% CI) 102 87 50.9% -0.03 [-0.19, 0.14]
Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)
LDL in adolescence
Lucas 1989c 2.7 0.7 59 2.5 0.6 66 27.6% 0.20 [-0.03, 0.43]
Lucas 1990c 2.7 0.6 38 2.8 0.6 39 21.5% -0.10 [-0.37, 0.17]
Subtotal (95% CI) 97 105 49.1% 0.06 [-0.24, 0.35]
Heterogeneity: Tau² = 0.03; Chi² = 2.77, df = 1 (P = 0.10); I² = 64%, CI for I² [0%, 92%]
Test for overall effect: Z = 0.39 (P = 0.70)
Total (95% CI) 199 192 100.0% 0.02 [-0.12, 0.15]
Heterogeneity: Tau² = 0.00; Chi² = 3.71, df = 3 (P = 0.29); I² = 19%, CI for I² [0%, 90%]
Test for overall effect: Z = 0.25 (P = 0.80)
-0.5 -0.25 0 0.25 0.5
Favours [Supplemented] Favours [Unsupplemented]
e.
Supplemented
Unsupplemented
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
SBP in childhood
Amesz 2010 104 7 33 105 7 21 8.5% -1.00 [-4.83, 2.83]
Fewtrell 2001 102.2 9.8 70 100.5 10.2 83 12.4% 1.70 [-1.48, 4.88]
Lucas 1989a 98.6 9.5 60 98.7 7.9 66 13.3% -0.10 [-3.17, 2.97]
Lucas 1989b 99.2 9.8 146 99.3 9.6 133 24.1% -0.10 [-2.38, 2.18]
Lucas 1990a 101.8 10.8 65 103.4 10.1 68 9.9% -1.60 [-5.16, 1.96]
Lucas 1990b 102.7 9.5 109 100.4 9.6 111 19.7% 2.30 [-0.22, 4.82]
Zachariassen 2011 106 10 79 105 10.1 71 12.1% 1.00 [-2.22, 4.22]
Subtotal (95% CI) 562 553 100.0% 0.50 [-0.62, 1.62]
Heterogeneity: Tau² = 0.00; Chi² = 4.94, df = 6 (P = 0.55); I² = 0%, CI for I² [0%, 65%]
Test for overall effect: Z = 0.88 (P = 0.38)
SBP in adolescence
Lucas 1989c 116.3 8 64 113.6 9 66 51.9% 2.70 [-0.23, 5.63]
Lucas 1990c 116.4 7.8 42 117.9 8 44 48.1% -1.50 [-4.84, 1.84]
Subtotal (95% CI) 106 110 100.0% 0.68 [-3.43, 4.79]
Heterogeneity: Tau² = 6.25; Chi² = 3.44, df = 1 (P = 0.06); I² = 71%, CI for I² [0%, 94%]
Test for overall effect: Z = 0.32 (P = 0.75)
-10 -5 0 5 10
Favours [Supplemented] Favours [Unsupplemented]

Fig 3. Forest plots of the effect of macronutrient supplements on secondary metabolic outcomes. (a) metabolic risks, (b) triglyceride concentrations, (c) HDL concentrations, (d) LDL concentrations, (e) SBP. Blue boxes in the forest plots represent the dichotomous data; green boxes represent the continuous data. CI, confidence interval; HDL, high-density lipoprotein; IV, inverse variance; LDL, low-density lipoprotein; M-H, Mantel-Haensel; SBP, systolic blood pressure; SD, standard deviation.

https://doi.org/10.1371/journal.pmed.1002952.g003

supplemented and unsupplemented groups (2 trials [16,28]; 201 children; MD 0.05 mmol/L; 95% CI −0.04 to 0.15 mmol/L; $P = 0.28$; Fig 3C). At >3 years, supplemented children had higher HDL concentrations than unsupplemented children (4 trials [16,28,32,40]; 391 children; MD 0.08 mmol/L; 95% CI 0.02–0.13 mmol/L; $P = 0.005$; Fig 3C).

There was no difference between supplemented and unsupplemented groups in LDL concentrations in childhood (2 trials [32,40]; 189 children; MD −0.03 mmol/L; 95% CI −0.19 to 0.14 mmol/L; $P = 0.75$; Fig 3D) or in adolescence (2 trials [16,28]; 202 children; MD 0.06 mmol/L; 95% CI −0.24 to 0.35 mmol/L; $P = 0.70$; Fig 3D) or at >3 years (4 trials [16,28,32,40]; 391 children; MD 0.02 mmol/L; 95% CI −0.12 to 0.15 mmol/L; $P = 0.80$; Fig 3D).

There was no difference between supplemented and unsupplemented groups for BMI in childhood (7 trials [16,22,28,32,40]; 1,136 children; MD −0.10 kg/m^2, 95% CI −0.37 to 0.16 kg/m^2; $P = 0.45$; S5A Fig) or in adolescence (2 trials [16,28]; 216 children; MD −0.48 kg/m^2, 95% CI −2.05 to 1.08 kg/m^2; $P = 0.55$; S5A Fig).

In childhood, supplemented children had lower fasting blood glucose concentrations than unsupplemented children (2 trials [32,40]; 189 children; MD −0.20 mmol/L; 95% CI −0.34 to −0.06 mmol/L; $P = 0.005$; S5B Fig). There was no clear difference between supplemented and unsupplemented groups in fasting blood glucose concentrations in adolescence (2 trials [16,28]; 216 children; MD −0.06 mmol/L; 95% CI −0.25 to 0.12 mmol/L; $P = 0.49$; S5B) or at >3 years (4 trials [16,28,32,40]; 405 children; MD −0.13 mmol/L, 95% CI −0.26 to 0.00 mmol/L; $P = 0.05$; S5B Fig).

There was no clear difference between supplemented and unsupplemented groups in fasting insulin concentrations in childhood (2 trials [32,40]; 189 children; MD 4.38 pmol/L; 95% CI −1.70 to 10.47 pmol/L; $P = 0.16$; S5C Fig), in adolescence (2 trials [16,28]; 216 children; MD −1.18 pmol/L; 95% CI −8.26 to 5.90 pmol/L; $P = 0.74$; S5C Fig), or at >3 years (4 trials [16,28,32,40]; 405 children; MD 2.02 pmol/L; 95% CI −2.59 to 6.64 pmol/L; $P = 0.39$; S5C Fig).

There was no clear difference between supplemented and unsupplemented groups in insulin resistance measured by Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) in childhood (1 trial; 39 children; standard mean difference [SMD] −0.13 pmol/L; 95% CI −0.77 to 0.51 pmol/L; $P = 0.69$; S5D Fig) or measured by fasting 32–33 split proinsulin in adolescence (2 trials [16,28]; 216 children; SMD −0.02 pmol/L; 95% CI −0.71 to 0.68 pmol/L; $P = 0.96$; S5D Fig) or at >3 years (3 trials [16,28,32]; 255 children; SMD −0.04 pmol/L; 95% CI −0.52 to 0.44 pmol/L; $P = 0.86$; S5D Fig).

There were no differences between supplemented and unsupplemented groups for SBP in childhood (7 trials [16,22,28,32,40]; 1,115 children; MD 0.50 mmHg; 95% CI −0.62 to 1.62 mmHg; $P = 0.38$; Fig 3E) or in adolescence (2 trials [16,28]; 216 children; MD 0.68 mmHg; 95% CI −3.43 to 4.79 mmHg; $P = 0.75$; Fig 3E); for diastolic blood pressure (DBP) in childhood (7 trials [16,22,28,32,40]; 1,115 children; MD 0.47 mmHg; 95% CI −0.45 to 1.39 mmHg; $P = 0.32$; S6A Fig) or in adolescence (2 trials [16,28]; 216 children; MD 1.78 mmHg; 95% CI −1.05 to 4.61 mmHg; $P = 0.22$; S6A Fig); or for mean arterial pressure (MAP) in childhood (3 trials [22,32,40]; 357 children; MD 0.95 mmHg; 95% CI −1.19 to 3.09 mmHg; $P = 0.39$; S6B Fig) or in adolescence (2 trials [16,28]; 216 children; MD 1.66 mmHg, 95% CI −3.44 to 6.75 mmHg; $P = 0.52$; S6B Fig).

Table 2. Summary of subgroup analyses.

	Subgroup	No. of participants (studies)	RR or MD (95% CI)	*P* for overall effect	I^2	*P* for subgroup interaction
Sex of infants						
Cognitive impairment in toddlers	Boys	116 (1 RCT) [27]	RR = 1.12 (0.74 to 1.70)	0.59	NA	0.19
	Girls	118 (1 RCT) [27]	RR = 1.83 (1.00 to 3.35)	0.05	NA	
Cognitive scores in toddlers	Boys	201 (2 RCTs) [16,33]	MD = 5.60 (1.07 to 10.14)	0.02	0%	0.03
	Girls	212 (2 RCTs) [16,33]	MD = −2.04 (−7.04 to 2.95)	0.42	0%	
Motor scores in toddlers	Boys	201 (2 RCTs) [16,33]	MD = 4.32 (−4.40 to 13.04)	0.33	88%	0.55
	Girls	212 (2 RCTs) [16,33]	MD = 1.04 (−5.13 to 7.21)	0.74	65%	
SBP in childhood	Boys	366 (4 RCTs) [16,28]	MD = 0.70 (−1.88 to 3.28) mmHg	0.59	36%	0.74
	Girls	382 (4 RCTs) [16,28]	MD = 0.08 (−2.46 to 2.62) mmHg	0.95	41%	
SGA infants						
Cognitive scores in toddlers	SGA	569 (5 RCTs) [16,22,24,28,39]	MD = −0.47 (−5.20 to 4.25)	0.84	65%	NA
Motor scores in toddlers	SGA	569 (5 RCTs) [16,22,24,28,39]	MD = 2.70 (−2.02 to 7.42)	0.26	70%	NA
SBP in childhood	SGA	267 (4 RCTs) [16,28]	MD = 0.53 (−3.05 to 4.11) mmHg	0.77	49%	NA
Timing of the supplements						
Cognitive impairment in toddlers	Started in the hospital	623 (3 RCTs) [16,27,29]	RR = 0.91 (0.58 to 1.45)	0.70	69%	0.24
	Across in-hospital and postdischarge periods	None				
	Started after hospital discharge	96 (2 RCTs) [34,36]	RR = 1.78 (0.65 to 4.93)	0.26	0%	
Motor impairment in toddlers	Started in the hospital	389 (2 RCTs) [16,29]	RR = 0.75 (0.61 to 0.93)	0.008	0%	0.57
	Across in-hospital and postdischarge periods	30 (1 RCT) [41]	RR = 2.65 (0.12 to 60.21)	0.54	NA	
	Started after hospital discharge	96 (2 RCTs[34,36]	RR = 1.30 (0.30 to 5.70)	0.73	18%	
Cognitive scores in toddlers	Started in the hospital	1415 (8 RCTs) [6,16,23,24,26,28–30]	MD = 1.51 (−0.23 to 3.25)	0.09	0%	0.23
	Across in-hospital and postdischarge periods	235 (1 RCTs) [22]	MD = −1.60 (−5.15 to 1.95)	0.38	NA	
	Started after hospital discharge	591 (6 RCTs) [33,34,36–39]	MD = −0.12 (−2.34 to 2.09)	0.91	0%	
Motor scores in toddlers	Started in the hospital	1415 (8 RCTs) [6,16,23,24,26,28–30]	MD = 2.04 (−0.08 to 4.16)	0.06	40%	0.48
	Across in-hospital and postdischarge periods	235 (1 RCT) [22]	MD = 0.30 (−2.77 to 3.37)	0.85	NA	
	Started after hospital discharge	591 (6 RCTs) [33,34,36–39]	MD = 0.15 (−2.55 to 2.86)	0.91	44%	
SBP in childhood	Started in the hospital	758 (4 RCTs) [16,28]	MD = 0.35 (−1.18 to 1.88) mmHg	0.66	18%	0.72
	Across in-hospital and postdischarge periods	153 (1 RCT) [22]	MD = 1.70 (−1.48 to 4.88) mmHg	0.29	0%	
	Started after hospital discharge	204 (2 RCTs) [32,40]	MD = 0.17 (−2.29 to 2.64) mmHg	0.89	0%	

Abbreviations: CI, confidence interval; MD, mean difference; NA, not applicable; RCT, randomised controlled trial; RR, relative risk; SBP, systolic blood pressure.

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Secondary health outcomes

Supplemented and unsupplemented toddlers were not different in the incidence of asthma (3 trials [16,27,28]; 1,011 children; RR 1.02; 95% CI 0.82–1.27; $P = 0.85$; S7A Fig) or eczema (2 trials [16,28]; 777 children; RR 0.96; 95% CI 0.72–1.28; $P = 0.80$; S7B Fig). None of the included trials reported other secondary health outcomes.

Subgroup analyses

Sex. In toddlers, there was no significant sex interaction for cognitive impairment [27]. However, supplemented boys had higher cognitive scores than unsupplemented boys (MD 5.60; 95% CI 1.07–10.14; $P = 0.02$), but there were no differences in girls [16,33] ($P = 0.03$ for interaction). There were no significant sex interactions for motor scores in toddlers [16,33] or SBP in childhood [16,28] (Table 2).

SGA infants. In children born SGA, there were no clear differences between supplemented and unsupplemented groups in cognitive scores in toddlers [16,22,24,28,39], motor scores in toddlers [16,22,24,28,39], or SBP in childhood [16,28] (Table 2).

Timing of the supplement. There were no clear differences between supplemented and unsupplemented groups in cognitive impairment in toddlers, cognitive scores in toddlers, motor scores in toddlers, and SBP in the different timing subgroups, and there was no evidence of an interaction between timing and effects of supplements on cognitive impairment in toddlers [16,27,29,34,36], motor impairment in toddlers [16,29,34,36,41], cognitive scores in toddlers [6,16,22–24,26,28–30,33,34,36–39], motor scores in toddlers [6,16,22–24,26,28–30,33,34,36–39], and SBP in childhood [16,22,28,32,40] (Table 2). Toddlers who had received supplements had a lower risk of motor impairment than the unsupplemented groups (RR 0.75; 95% CI 0.61–0.93; $P = 0.008$) if they received the supplements in hospital, but not if they received supplements both in-hospital and post discharge, or only post discharge (Table 2).

Due to insufficient data, we were unable to undertake other preplanned subgroup analyses (S2 Appendix).

Studies not included in quantitative synthesis

Agosti 2003 [31] reported no difference in overall Griffiths Mental Development Status (GMDS) scores at 12 months between supplemented (mean score = 101) and unsupplemented groups (mean score = 102). In subgroup analyses, supplemented SGA children had better GMDS scores than unsupplemented at 6 months (mean scores 101 versus 95), but the differences did not persist at 9 and 12 months. Supplemented boys also had better GMDS scores than unsupplemented at 6 months (mean scores 102 versus 98) and 9 months (mean scores 106 versus 103) but not 12 months, whereas there was no difference in GMDS scores in supplemented and unsupplemented girls at each age.

Cooper 1988 [25] reported no difference in the overall GMDS scores between supplemented and unsupplemented toddlers (MD 5; 95% CI −21.83 to 11.83; $P = 0.56$).

Friel 1993 [35] reported no difference in GMDS at 12 months between supplemented and unsupplemented groups (mean score 92 versus 90).

Quality of evidence (GRADE)

There were no data for the outcomes: composite of survival free of any disability, school performance, elevated fasting plasma glucose concentrations at >3 years, and insulin resistance at >3 years. The quality of the evidence was assessed as low or very low for all other development and metabolic outcomes (Table 3).

Table 3. GRADE table: Summary of findings.

Supplemented compared to unsupplemented nutrition for children born preterm or SGA					
Patient or population: Children born preterm or SGA					
Setting: Hospital or NICU					
Intervention: Supplemented nutrition					
Comparison: Unsupplemented nutrition					
	Anticipated absolute effects* (95% CI)				
Outcomes	**Risk with unsupplemented nutrition**	**Risk with supplemented nutrition**	Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
a. Summary of findings for the developmental outcomes					
Cognitive impairment in toddlers (primary outcome)	274 per 1,000	**274 per 1,000** (184 to 409)	**RR 1.00** (0.67 to 1.49)	719 (5 RCTs)	⊕○○○ VERY LOW [a,b,c,d]
Cognitive scores in toddlers	Comparator	Mean cognitive score in the intervention group was 0.57 points higher (0.71 lower to 1.84 higher)		2,241 (15 RCTs)	⊕⊕○○ LOW [a,b,d]
Motor impairment in toddlers	432 per 1,000	**328 per 1,000** (268 to 406)	**RR 0.76** (0.62 to 0.94)	515 (5 RCTs)	⊕○○○ VERY LOW [a,b,d,e]
Motor scores in toddlers	Comparator	Mean motor score in the intervention group was 1.16 points higher (0.32 lower to 2.65 higher)		2,241 (15 RCTs)	⊕⊕○○ LOW [a,b,d]
Cerebral palsy in toddlers	48 per 1,000	**45 per 1,000** (28 to 74)	**RR 0.95** (0.59 to 1.55)	1,341 (4 RCTs)	⊕⊕○○ LOW [c,d]
b. Summary of findings for the metabolic outcomes					
Overweight/obesity at >3 years	169 per 1,000	127 per 1,000 (57 to 275)	RR 0.75 (0.34 to 1.63)	150 (1 RCT)	⊕⊕○○ LOW [a,c,f]
Triglyceride at >3 years (mmol/L)	Comparator	The mean triglyceride concentration in the intervention group was 0.04 mmol/L lower (0.31 lower to 0.24 higher)		391 (4 RCTs)	⊕○○○ VERY LOW [d,g,h]
HDL at >3 years (mmol/L)	Comparator	The mean HDL concentration in the intervention group was 0.08 mmol/L higher (0.02 higher to 0.13 higher)		390 (4 RCTs)	⊕⊕○○ LOW [d,g]
LDL at >3 years (mmol/L)	Comparator	The mean LDL concentration in the intervention group was 0.02 mmol/L higher (0.12 lower to 0.15 higher)		391 (4 RCTs)	⊕⊕○ LOW [d,g]
SBP at >3 years (mmHg)	Comparator	The mean SBP in the intervention group was 0.5 mmHg higher (0.62 lower to 1.62 higher)		1,115 (7 RCTs)	⊕⊕○ LOW [d,g]

GRADE Working Group grades of evidence are as follows. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Uncertainty about methods used to generate a random sequence, conceal allocation or blind outcome assessors in some studies.

[b]Baseline characteristics were not balanced in some studies.

[c]CI includes both possible benefit and no benefits from supplementation.

[d]Some of the studies were supported by formula or fortifier companies whose role was not specified.

[e]One study was at high risk of selective reporting bias (infants with cerebral palsy were not included).

[f]Relatively few studies with few participants.

[g]Large losses to follow-up in childhood or beyond.

[h]Substantial heterogeneity existed.

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Abbreviations: CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MD, mean difference; NICU, neonatal intensive care unit; RCT, randomised controlled trial; RR, relative risk; SBP, systolic blood pressure; SGA, small for gestational age

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Discussion

We hypothesised that early macronutrient supplements of infants born small would benefit early cognition, but this may be at the cost of worse later metabolic outcomes. In our systematic review and meta-analysis of 21 RCTs and 1 quasi-RCT involving 3,680 infants, we found no evidence that early macronutrient supplementation led to significant changes in cognitive function in children born preterm or SGA. This finding from randomised trials is in contrast to previous observational studies [42,43] that suggest a positive association between macronutrient intake and cognitive development in preterm infants. However, we found limited evidence that early macronutrient supplements decreased the risk of motor impairment in toddlers and, contrary to our hypothesis, improved some metabolic outcomes in childhood. Despite the large numbers of trials and infants included, the evidence is limited by the overall low methodological quality, substantial heterogeneity, and few measures of outcomes after 3 years of age.

Our findings that supplementation decreased the risk of motor impairment in toddlers but did not change motor scores appear contradictory. There are several possible reasons for this. Firstly, the mean scores may not reflect children whose scores fall below specified cut-off points, particularly if data are not normally distributed. Secondly, 15 trials with 2,241 toddlers reported motor scores, but only 5 trials with 515 toddlers reported motor impairment, and only 4 of these reported both motor scores and the incidence of motor impairment. In each of these 4 trials, the differences between supplemented and unsupplemented nutrition groups were in the same direction for both impairments and mean scores. However, the overall finding of decreased motor impairment was dominated by one trial [16] (weighted 64%, Fig 2C), although in the analysis of motor scores, this trial was only weighted 8.3%. Furthermore, the finding of decreased motor impairment was limited by very low-quality evidence. Therefore, we would recommend reporting both scores and numbers of impaired children in future studies.

The effects of macronutrient supplements on developmental outcomes in childhood or later were unclear. Only 1 trial [27] reported cognitive impairment, 2 [32] reported cognitive scores, and 1 [32] reported motor scores in childhood; none reported differences between supplemented and unsupplemented children. This limited evidence suggests that although macronutrient supplements may improve early motor but not cognitive development, these effects may not persist in later life.

Contrary to our hypothesis, we did not find evidence of increased adverse cardiometabolic risk factors after early macronutrient supplementation; rather, we found that children in the supplemented groups had higher HDL concentrations in childhood. Others [44,45] have reported an inverse association between HDL cholesterol concentrations in childhood and cardiometabolic risks in adulthood. However, mean HDL concentrations in both supplemented and unsupplemented groups in our systematic review were below the 10th percentile (2.2 mmol/L) [46], suggesting that all included children are at increased risk of cardiometabolic disease but that those in the unsupplemented groups might be at greater risk.

We also found that supplemented children had lower fasting blood glucose concentrations than unsupplemented children. Childhood fasting blood glucose concentrations are inversely related to pre-diabetes and diabetes in adulthood, especially if the glucose concentration is above 4.7 mmol/L [47]. The mean fasting blood concentrations in studies included in this review were close to or above this threshold, again suggesting that both groups may be at increased risk of later diabetes but that the unsupplemented group might be at greater risk. We also did not detect differences in other metabolic risk factors or blood pressure between supplemented and unsupplemented groups in childhood or in adolescence. Thus, the evidence

from this review of randomised trials suggests that, contrary to findings from observational studies [13,44,45], early macronutrient supplementation of preterm and SGA infants does not have adverse effects on later metabolic outcomes.

Interpretation of these findings is limited by heterogeneity and the small number of trials reporting longer-term outcomes. Some of the heterogeneity may be due to the different types of interventions. For example, for the analysis of triglyceride concentrations in childhood, infants in one trial were fed formula [32] and in the other fed breast milk [40] as the main diet. Similarly, for the analysis of metabolic outcomes and blood pressure in adolescence, one trial compared preterm formula with banked breast milk as sole diet or supplement, while the other compared preterm formula with term formula [16]. Because breastfeeding itself has been associated with lower later blood pressure and risk of obesity [48–50], this may contribute to the heterogeneity in these results, although the breastfeeding studies are also observational and potentially confounded by the social determinants of these health outcomes.

In the subgroup analyses, based on limited data, we found that in toddlers, supplemented compared with unsupplemented boys had no difference in the incidence of cognitive impairment, but had a 5.6-point advantage on cognitive scores (95% CI 1.07–10.14). However, there was no difference in cognitive scores between supplemented and unsupplemented girls. A sex-specific response to early nutrient supplements has also been reported in animal studies [51,52]. However, few studies of nutritional supplements in infants born small have reported outcomes separately for boys and girls. A planned individual participant data (IPD) meta-analysis (PROSPERO CRD42017072683) may prove helpful to further explore possible sex differences in the effects of macronutrient supplements in human infants born small.

In the subgroup of infants born SGA, there appeared to be no effect of supplements on cognitive and motor scores in toddlers,or SBP in childhood. However, only 5 trials reported this subgroup separately, and there was substantial heterogeneity. In one trial [24], the unsupplemented group was of higher birth weight and gestational age than the supplemented group, although heterogeneity was still substantial after exclusion of this trial.

In the subgroup analysis of different timing of supplements, there was again no difference in cognitive impairment, but toddlers in the supplemented group had better motor development only when the intervention was given in hospital. Furthermore, timing of supplements may have contributed to the substantial heterogeneity in the subgroup analyses of motor scores of boys and girls separately. Boys who received supplemented nutrition during initial hospitalisation had better motor scores than unsupplemented boys [16], but those who received supplemented nutrition after hospital discharge did not [33]. The in-hospital period aligns with the third trimester of gestation, when there is extensive fetal brain development, and the brain accounts for 60% of total oxygen and caloric consumption. Adequate nutrients are therefore most likely to be important to support brain development during this critical period [53,54]. These findings in one subgroup must be interpreted with caution but may suggest that providing preterm and SGA infants with supplemented nutrition during initial hospitalisation rather than later is more likely to benefit later developmental outcomes.

Three previous systematic reviews have compared the effect of supplemented versus unsupplemented formula started after hospital discharge, fortified versus unfortified breastmilk started in hospital or after hospital discharge [11,17,18]. Each identified a different single eligible trial reporting developmental outcomes [6,37,38]. All 3 trials reported no differences in cognitive and motor scores at 18 months, and none reported long-term metabolic or developmental outcomes after this age. Our study included all eligible trials regardless of type and timing of intervention and included all 3 of the previously reported trials plus another 19 trials, allowing more extensive analysis of some long-term outcomes.

There were some limitations to our study. The quality of evidence was low in many trials. Most were conducted more than 20 years ago, and the findings were not reported according to current guidelines. In particular, methodological details, including blinding of outcome assessment and the role of commercial sponsors, were unclear. Most trials were at high risk of attrition bias, which may introduce bias and loss of power [55] so that there can be limited confidence in the effect estimates. However, in the sensitivity analysis for cognitive and motor scores including only high-quality trials, the results were in the same direction, suggesting that this may not be major source of bias. There was a wide variety of interventions used, including different timing, type, duration, and routes of supplementation and substantial heterogeneity of findings. In addition, some studies reported multiple outcomes, and some research teams reported several different studies, which may result in a lack of independence that is not accounted for in our analyses. Furthermore, we analysed multiple outcomes, multiple time points, and a large number of subgroups, which increases the risk of type 1 error [56], and the subgroup findings in particular should be interpreted with caution.

Although 22 trials have been undertaken involving >3,000 infants, data regarding the effects of early macronutrient supplements on long-term developmental and metabolic outcomes are limited. In addition to new trials, longer-term follow-up of previous trials would provide critical evidence about the effect of macronutrients on long-term developmental and metabolic outcomes of preterm and SGA infants.

Contrary to the findings from observational studies, current low-quality evidence from randomised trials suggests that early macronutrient supplementation of infants born small does not alter later cognition but may decrease motor impairment in toddlers and improve some metabolic outcomes in childhood.

Supporting information

S1 Checklist. PRISMA checklist. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
(DOC)

S1 Appendix. List of outcomes.
(DOCX)

S2 Appendix. List of planned subgroup analyses.
(DOCX)

S3 Appendix. List of all references of included studies.
(DOCX)

S1 Table. Search strategy.
(DOCX)

S1 Fig. Risk of bias. (a) Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (b) Risk bias summary: review authors' judgements about each risk of bias item for each included study.
(TIF)

S2 Fig. Sensitivity analyses. Forest plots of effect of macronutrient supplementation on cognitive scores and motor scores including trials with low risk of bias. (a) Cognitive scores, (b) motor scores.
(TIF)

S3 Fig. Funnel plots. Funnel plots of supplemented versus unsupplemented nutrition for the outcomes of cognitive and motor scores in toddlers. (a) Cognitive scores, (b) motor scores. The middle dashed line indicates the overall MD. The dashed lines either side represent the pseudo 95% CIs. MD, mean difference.
(TIF)

S4 Fig. Forest plots of the effect of macronutrient supplementation on other developmental outcomes in toddlers. (a) Visual impairment, (b) hearing impairment.
(TIF)

S5 Fig. Forest plots of the effects of macronutrient supplementation on other metabolic outcomes. (a) BMI, (b) fasting blood glucose concentrations, (c) fasting insulin concentrations, (d) insulin resistance. BMI, body mass index.
(TIF)

S6 Fig. Forest plots of the effects of macronutrient supplementation on blood pressure. (a) DBP, (b) MAP. DBP, diastolic blood pressure; MAP, mean arterial pressure.
(TIF)

S7 Fig. Forest plots of the effects of macronutrient supplementation on asthma and eczema in toddlers. (a) Asthma, (b) eczema.
(TIF)

S1 Protocol.
(DOCX)

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