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Fat supplementation of human milk for promoting growth in preterm infants (Review)

Amissah EA, Brown J, Harding JE

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[Intervention Review]

Fat supplementation of human milk for promoting growth in preterm infants

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ABSTRACT

Background

As preterm infants do not experience the nutrient accretion and rapid growth phase of the third trimester of pregnancy, they are vulnerable to postnatal nutritional deficits, including of fat. Consequently, they require higher fat intakes compared to their full term counterparts to achieve adequate growth and development. Human milk fat provides the major energy needs of the preterm infant and also contributes to several metabolic and physiological functions. Although human milk has many benefits for this population, its fat content is highly variable and may be inadequate for their optimum growth and development. This is a 2020 update of a Cochrane Review last published in 2000.

Objectives

To determine whether supplementation of human milk with fat compared with unsupplemented human milk fed to preterm infants improves growth, body composition, cardio-metabolic, and neurodevelopmental outcomes without significant adverse effects.

Search methods

We used the standard search strategy of Cochrane Neonatal to search Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 8) in the Cochrane Library and MEDLINE via PubMed on 23 August 2019. We also searched clinical trials databases and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Published and unpublished randomised controlled trials were eligible if they used random or quasi-random methods to allocate preterm infants fed human milk in hospital to supplementation or no supplementation with additional fat.

Data collection and analysis

No new randomised controlled trials matching the selection criteria were found but we extracted data from the previously included trial due to changes in review outcomes from when the protocol was first published. Two reviewers independently abstracted data, assessed trial quality, and the quality of evidence at the outcome level using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. We planned to perform meta-analyses using risk ratio (RR) for dichotomous data and mean difference (MD) for continuous data, with their respective 95% confidence intervals (CIs). We planned to use a fixed-effect model and to explore potential causes of heterogeneity via sensitivity analyses.

Main results

One randomised trial involving 14 preterm infants was included. This risk of bias was unclear for all methodological domains. Very low-quality evidence means that there is uncertainty about the effect of fat supplemention on in-hospital rates of growth in weight (MD 0.6 g/

kg/day, 95% CI −2.4 to 3.6; 1 RCT, n = 14 infants,), length (MD 0.1 cm/week, 95% CI −0.08 to 0.3; 1 RCT, n = 14 infants) and head circumference (MD 0.2 cm/week, 95% CI −0.07 to 0.4; 1 RCT n = 14 infants), and on the risk of feeding intolerance (RR 3.0, 95% CI 0.1 to 64.3; 1 RCT, n = 16 infants). No data were available regarding the effects of fat supplementation on the risk of necrotising enterocolitis or neurodevelopmental outcomes.

Authors' conclusions

The one included trial suggests no evidence of an effect of fat supplementation of human milk on short-term growth and feeding intolerance in preterm infants. However, the very low-quality evidence, small sample size, few events, and low precision diminishes our confidence that these results reflect the true effect of fat supplementation of human milk in preterm infants, and no long-term outcomes were reported. Further high-quality research should evaluate the effect on growth, neurodevelopmental and cardio-metabolic outcomes in the context of the development of multicomponent fortifiers.

PLAIN LANGUAGE SUMMARY

Fat supplementation of human milk for promoting growth in preterm infants

Review question

We reviewed the evidence to determine whether addition of extra fat (supplements) to human milk fed to infants born early (preterm) compared with no additional fat improves growth, body fat, obesity, heart problems, high blood sugar, and brain development, without significant side effects.

Background

Preterm babies at birth lack adequate fat stores because they are born before laying down nutrient stores in the rapid growth phase of the third trimester of pregnancy. Consequently, they require higher fat intakes compared to their full term counterparts to achieve adequate growth and development. Fat provides approximately half of the calories in human milk and supports growth and brain development. Although human milk has many benefits for the preterm baby, it may contain variable and insufficient quantities of fat for adequate growth and development. Inadequate supply of fat in preterm infants fed human milk may adversely affect their growth and development. Therefore, additional fat may be added to human milk, usually by adding commercially prepared fat mixtures to a small amount (e.g. 20 mL) of expressed breast milk.

Study characteristics

We included one trial with very low-quality evidence and involving 14 preterm infants. The search is up to date as of August 2019.

Key results

Addition of extra fat to human milk for preterm infants showed no clear benefits with regards to short-term rates of weight gain, length gain, and head growth. There was no evidence that the extra fat increased the risk of feeding intolerance. No data were available regarding the effects of addition of extra fat on long-term growth, body fat, obesity, high blood sugar, or brain development. There were also limited data to assess side effects.

Conclusions

There was insufficient high-quality evidence on the benefits and harms of the addition of extra fat to human milk in preterm infants, and no long-term outcomes have been reported. Since addition of extra fat to human milk is currently done as part of multi-nutrient fortification, future trials should evaluate the effect of the fat component on short- and long-term growth, body fat, obesity, high blood sugar, or brain development. The right amount and composition of extra fat needed, side effects, and delivery practices should also be evaluated.

Summary of findings 1. Fat supplementation compared to control for promoting growth in preterm infants

Fat supplementation compared to control for promoting growth in preterm infants

Patient or population: preterm infants
Setting: two neonatal units in Sweden
Intervention: fat supplementation of human milk
Comparison: unsupplemented human milk

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Fat supplementation				
Growth - weight - weight gain (g/kg/day)	The mean weight gain in the unsupplemented human milk group was 15.3 g/kg/day.	MD 0.6 g/kg/day higher (2.4 lower to 3.6 higher)	-	14 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	
Growth - length - length gain (cm/week)	The mean length gain in the unsupplemented human milk group was 0.8 cm/week.	MD 0.1 cm/week higher (0.08 lower to 0.3 higher)	-	14 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	
Growth - head circumference - head growth (cm/week)	The mean head growth in the unsupplemented human milk group was 0.9 cm/week.	MD 0.2 cm/week higher (0.07 lower to 0.4 higher)	-	14 (1 RCT)	⊕⊖⊖⊖ Very low [1,2]	
Neurodevelopmental outcomes	-	-	-	-	-	None of the included studies reported on neurodevelopmental outcomes.
Duration of hospital admission (days)	-	-	-	-	-	None of the included studies reported on duration of hospital admission.
Feeding intolerance	0 per 1000	0 per 1000 (0 to 0)	RR 3.00 (0.1 to 64.3)	16 (1 RCT)	⊕⊖⊖⊖ Very low [1,3]	.

Necrotising enterocolitis	-	-	-	-	-	None of the included studies reported on necrotising enterocolitis.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio;

GRADE Working Group grades of evidence
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

[1] Downgraded one level for risk of bias: most of the trials lacked methodological details
[2] Downgraded one level for imprecision: few participants, wide confidence intervals, which include meaningful benefit and harm
[3] Downgraded two levelsfor serious imprecision: few participants, few events, wide confidence intervals, which include meaningful benefit and harm

BACKGROUND

Description of the condition

Preterm infants are born with inadequate fat stores, due to their being born before the nutrient accretion and rapid growth phase of the third trimester of pregnancy (Robinson 2017). They also have higher nutrient requirements than term infants in the early postnatal period (Fenton 2013). Fat in human milk provides the major energy needs (45% to 55%) of the preterm infant and also contributes to several metabolic and physiological functions paramount to their growth, health, and development (Delplanque 2015). In particular, derivatives of long-chain polyunsaturated fatty acids (LCPUFA), arachidonic acid (AA), and docosahexaenoic acid (DHA), play key roles in normal immune system functioning as well as brain and retinal development (Delplanque 2015; Hadley 2016; Lapillonne 2014). Thus, insufficient consumption of fat in the preterm infant may have adverse effects on their growth, immune development, neurologic function, and visual acuity (Georgieff 2005; Innis 2003).

Human milk, the preferred enteral nutrition for preterm infants, optimises immunity, visual acuity (Section on Breastfeeding 2012), gastrointestinal function, and neurodevelopmental outcomes in preterm infants (Isaacs 2009; Underwood 2013). In contrast to infant formula, it contains a full array of polyunsaturated fatty acids, including DHA and AA (Moon 2016).

However, in spite of its immense benefits, unsupplemented human milk is nutritionally inadequate for preterm infants for several reasons. Firstly, human milk has insufficient quantities of many nutrients needed for the rapid growth of preterm infants (Su 2014) and its nutrient concentrations fluctuate over time, with fat being the most variable nutrient (Patel 2016). It shows intra- and inter-individual variations (Bhatia 2016), and varies according to maternal diet, time of day, and during a breastfeeding session, with hind milk richer in fat than foremilk (Innis 2014).

Secondly, important reductions in fat concentrations of human milk have been reported during processes of storage, freezing, thawing, and pasteurisation, due to adherence of the disrupted fat globules to container surfaces (Chang 2012; Stocks 1985; Vieira 2011).

Further, breastfeeding initiation and continuation in mothers of preterm infants is not always feasible. Early preterm birth can hinder maternal breast development, delay secretory activation and potentially diminish milk production (Geddes 2013). While these limitations could result in a reliance on donor human milk from mothers who gave birth at term, pasteurisation of donor human milk may inactivate the two endogenous lipases of human milk (lipoprotein lipase and bile salt-stimulated lipase), thus decreasing lipid absorption and reduce weight gain (Arslanoglu 2013; Peila 2016). Medium-chain triglyceride (MCT) supplements are sometimes added to donor milk, as these do not require bile salts or pancreatic lipase for digestion and are more easily absorbed than LCPUFA (Kenner 2014). However, this does not provide the high requirements for LCPUFA to optimise brain and retinal development of preterm infants.

A limited supply of fat in preterm infants fed human milk may adversely affect their growth and development. Therefore, additional fat in the form of a supplement may be added to human milk.

Description of the intervention

Enteral fat supplements are available as commercial modular products such as microlipids and medium-chain triglyceride (MCT) oils (Choi 2016; Yang 2013), a blend of more than one oil including high fat polyunsaturated fatty acid (HF-PUFA) (Younge 2017) or as multicomponent products like liquid human milk fortifiers (LHMF) (Berseth 2014). They are mixed with human milk and fed enterally to preterm infants once they begin to tolerate breast milk feeds (Berseth 2014). Some of these supplements can also be used via the parenteral route as lipid emulsions (Martin 2015).

Depending on the intended effect, some formulations may contain more than one source of fat supplements that may be combined into the same principal compartment or used together from different compartments. For example, enteral micro lipid and fish oil have recently been successfully combined as a mechanism to reduce intralipid use in a preterm infant with an enterostomy (Yang 2013). Thus, combining different sources of fat supplements may have important maintenance or therapeutic effects. However, the accumulation of certain fatty acids may inhibit the metabolism of others, and cause elevated lipid levels. For example, omega-3 and omega-6 lipids compete for the same desaturase enzyme. Thus, a balanced ratio between them is important (Hadley 2016).

How the intervention might work

Paradoxically, in spite of their high need for fat intake per kg body weight, preterm infants present unique challenges that interfere with the delivery of fat (Martin 2015). Preterm infants have low level of activity of pancreatic lipase and bile salt-stimulated lipase which are normally responsible for a substantial part of fat digestion, micelle formation, and fat absorption (Lindquist 2010). As a result, preterm infants may experience maldigestion and malabsorption of enteral fats, leading to potential intestinal inflammation and injury, loss of energy, and inadequate fat store accumulation (Howles 1999; Martin 2015). Human milk, unlike formula, contains bile salt-stimulated lipase which enhances the digestion and absorption of milk fat (Martin 2015). Therefore, fat supplementation of human milk is expected to increase fatty acid bioavailability and alleviate dietary deficiency of fat.

Additionally, the unique properties of the different formulations of fat supplements are expected to enhance therapeutic outcomes (Deshpande 2011). For example, MCTs, unlike long-chain fatty acids, do not require carnitine to enter the mitochondria and so are oxidised rapidly to ketone bodies, making them a quick and readily available source of energy (Longo 2016).

Furthermore, the chain length and saturation of fatty acids impact their absorption (Delplanque 2015). MCTs, whose hydrolysis is independent of the availability of bile and lipase, are more efficiently absorbed than long-chain fatty acids, making them useful for infants with impaired digestion and absorption of fat, including preterm infants (Martin 2015).

Finally, complications from fat supplementation can also occur. For example, in a study conducted in mice, MCT fortifiers were reported to promote allergic sensitisation and anaphylaxis (Li 2013), while formula supplemented with MCTs is associated with

higher osmolality and a higher risk of osmotic diarrhoea (Pereira-da-Silva 2008).

Why it is important to do this review

Dietary fat is vital for energy, growth, and long-term health in preterm infants. However, the previous version of this review found no clear evidence of benefits or harms of fat supplementation of human milk in preterm infants (Kuschel 2000). Interest in fat supplementation of human milk has grown to include not just the digestibility of the fat supplement, but also its quality and role in the visual and neural development of the preterm infant (Koletzko 2014). Thus, it was important to update the review with the most recent trials assessing these effects, including those with LCPUFA supplements.

OBJECTIVES

To determine if supplementation of human milk with fat compared with unsupplemented human milk fed to preterm infants improves growth, body composition, cardio-metabolic and neurodevelopmental outcomes without significant adverse effects.

METHODS

Criteria for considering studies for this review

Types of studies

Published and unpublished controlled trials utilising either random or quasi-random patient allocation were considered for inclusion in this review. Cross-over trials were excluded.

Types of participants

Preterm infants (< 37 weeks' gestation) receiving enteral feeding of human milk within a hospital setting.

Types of interventions

Human milk with or without additional fat supplementation. Micronutrient and vitamin supplements were allowed in both groups.

Types of outcome measures

The primary and secondary outcomes for this review were aligned with the outcomes of the Cochrane Review Multi-nutrient fortification of human milk for preterm infants (Brown 2016).

Primary outcomes

- Growth: weight, length, head circumference, skinfold thickness (WHO 1995), body mass index, and measures of body composition (lean/fat mass) and growth restriction (proportion of infants who remained < 10th percentile for the index population distribution of weight, length, or head circumference). Growth parameters were assessed from birth to hospital discharge, at or after two years' corrected age, during adolescence, and as adults.
- Neurodevelopmental outcomes: neurodevelopmental outcomes after 12 months post term included neurological evaluations, developmental scores, and classifications of disability, including auditory and visual disability. We defined neurodevelopmental impairment as the presence of one or more of the following: non-ambulant cerebral palsy, developmental quotient more than two standard deviations below the population mean, blindness (visual acuity < 6/60) or deafness (any hearing impairment requiring or unimproved by amplification).

Secondary outcomes

- Duration of hospital admission (days);
- Feeding intolerance that resulted in cessation or reduction in enteral feeding;
- Necrotising enterocolitis (NEC);
- Diarrhoea;
- Serum bilirubin concentrations;
- Long-term measures of cardio-metabolic health such as insulin resistance, obesity, diabetes, and hypertension.

Search methods for identification of studies

We used the criteria and standard methods of Cochrane and Cochrane Neonatal (see the Cochrane Neonatal search strategy for specialised register).

Electronic searches

We conducted a comprehensive search including: Cochrane Central Register of Controlled Trials (CENTRAL 2019, Issue 8) in the Cochrane Library and MEDLINE via PubMed (2018 to 23 August 2019). We have included the search strategies for each database in Appendix 1. We did not apply language restrictions.

We searched clinical trial registries for ongoing or recently completed trials (ISRCTN Registry). The World Health Organization's International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/) and the U.S. National Library of Medicine's ClinicalTrials.gov (clinicaltrials.gov) were searched via Cochrane CENTRAL.

This search updates the searches conducted for previous versions of the review (Amissah 2018, Kuschel 2000).

Searching other resources

We also searched the reference lists of any articles selected for inclusion in this review in order to identify additional relevant articles. We did not search any additional conference proceedings.

Data collection and analysis

We used the guidelines and standardised methods of the Cochrane Neonatal Collaborative Review Group to assess the methodological quality of the included trials.

Selection of studies

We identified 907 records from the searches for this review. For the 2018 update, two authors (EA and JB) independently applied the eligibility criteria to the records identified by the searches. We resolved any disagreements arising through discussions. However, none of the new studies identified were relevant to this review.

For the 2020 update, Cochrane Neonatal screened the titles and abstracts identified by the search independently and in duplicate in consultation with a review author (JH).

Data extraction and management

No new trials were included in the review but, due to changes in our primary and secondary outcomes from the last published protocol (1997), two authors (EA and JB) independently extracted data from the previously included trial. We used a data extraction form which was developed prior to data gathering. Data such as source details, study eligibility, study design, participant characteristics, and intervention and control details were extracted. We planned to resolve conflicts in the data extraction and management process by referral to a third author. The data were then exported into Cochrane's statistical software, Review Manager 2014 (Review Manager 2014).

Assessment of risk of bias in included studies

Two review authors (EA and JB) independently assessed the risk of bias (low, high, or unclear) of the included trials using the Cochrane 'Risk of bias' tool (Higgins 2017) for the following domains:

- Sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Any other bias

Any disagreements were resolved by discussion or by a third assessor. See Appendix 2 for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We used the numbers of events in the control and intervention groups of the study to calculate the risk ratio (RR) with 95% confidence intervals (CIs) for dichotomous data. We calculated mean differences (MDs) between treatment groups where outcomes were measured in the same way for continuous data. We did not need to use standardised mean differences (SMD) in this update, although we planned to use it where outcomes from trials were the same but different methods had been used to collect the data. We reported 95% CIs for all outcomes. We did not calculate numbers needed to treat for an additional beneficial outcome (NNTBs) or the numbers needed to treat for and additional harmful outcome (NNTHs) due to insufficient data.

Unit of analysis issues

We did not identify any unit of analysis issues. We planned to undertake analysis at the individual level taking clustering into account as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* if we had identified cluster-randomised trials (Higgins 2017).

Dealing with missing data

We noted levels of attrition. We carried out analyses using an intention-to-treat basis, where possible, for all of the outcomes. We analysed all participants, where possible, in the treatment group to which they were randomised, regardless of the actual treatment received. As we had only one included trial, we were unable to conduct sensitivity analyses and were unable to address the potential impact of missing data on the findings of the review.

Assessment of heterogeneity

We planned to assess whether the clinical and methodological characteristics of the included studies were sufficiently similar for meta-analysis to provide a clinically meaningful summary. We planned to do this by assessing statistical heterogeneity using the Chi^2 test and the I^2 statistic. An I^2 measurement greater than 50% and a low P value (< 0.10) in the Chi^2 test for heterogeneity was taken to indicate moderate-to-high heterogeneity. Where substantial heterogeneity was detected, we planned to explore possible explanations in sensitivity or subgroup analyses, or both. We planned to take statistical heterogeneity into account when interpreting the results, especially if there was any variation in the direction of effect. We were unable to perform any of these assessments as we included only one trial .

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Some types of reporting bias (e.g. publication bias, multiple publication bias, language bias) reduce the likelihood that all studies eligible for a review will be retrieved. If all eligible studies are not retrieved, the review may be biased.

We aimed to conduct a comprehensive search for eligible studies and were alert for duplication of data. We were unable to assess publication bias through the creation of funnel plots as there were insufficient studies for any of the outcomes (10 or more trials required).

Data synthesis

Quality of evidence

We used the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes: growth, neurodevelopment, duration of hospital admission, feeding intolerance that results in cessation or reduction in enteral feeding, and necrotising enterocolitis.

Two authors (EA and JB) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from randomised controlled trials as high-quality but downgraded the evidence one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates, and presence of publication bias. We used the GRADEpro GDT Guideline Development Tool to create a 'Summary of findings' table to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence in one of four levels:

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: 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: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup and sensitivity analyses if moderate-to-high heterogeneity was identified. We planned to consider whether an overall summary was meaningful and if it was, we planned to use a random-effects model to analyse it. We planned to carry out the following subgroup analyses to evaluate differences in outcome between: gestational age subgroups (< 30 versus 30 to < 34 versus 34 to < 37 completed weeks), birth weight subgroups (< 1 kg versus ≥1 kg), male versus female sex; and types of fat supplements (MCT versus other forms). However, there were insufficient data to allow us to conduct any subgroup analyses.

Sensitivity analysis

We planned to conduct sensitivity analysis by examining only those trials considered to have a low risk of bias for allocation concealment and randomisation. We were unable to do this as only one trial was included in the review.

RESULTS

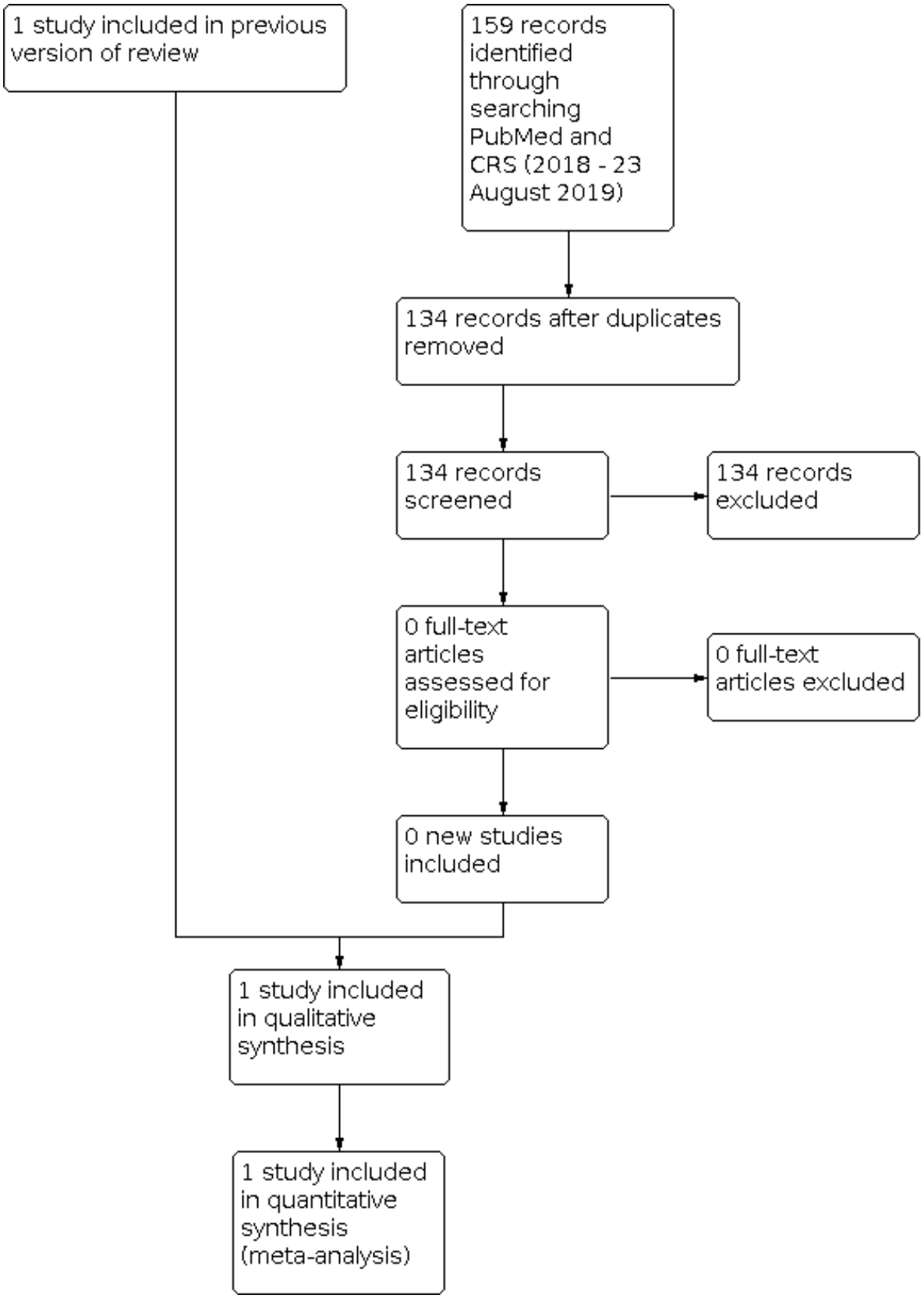
Description of studies

Regarding study details please see: Included studies; Excluded studies.

Results of the search

A search of 1368 records yielded no new trials. However, one trial from the previous review (published in 1999) was included in the 2018 update of this review (Polberger 1989). For a full description of our searches, please see 'Study flow diagram' (Figure 1).

Figure 1. Study flow diagram: review update



Included studies

Data were extracted from a full-text publication for the only trial included in this review (Polberger 1989). This four-armed randomised controlled trial included 28 randomised preterm infants, of whom 14 fulfilled our predefined criteria. The trial was conducted at two centres in Sweden and was published in English. Details of the included trial are summarised in the table Characteristics of included studies.

Participants

The trial examined preterm infants < 32 gestational weeks and of birth weight < 1500 grams. The infants had no medical problems or major congenital malformations.

Interventions

Standardised rather than targeted fortification was used and infants were randomised to receive either fat (1 gram human milk fat per 100 mL of human milk) or no supplementation. Two other arms of the study evaluated supplementation with protein alone and protein combined with fat, and were excluded from this review. The intervention was commenced once the infants were tolerating enteral feeds at 170 mL/kg/day and was stopped when the infants were breastfed or weighed 2200 grams. Both maternal and donor breast milk were used and supplemental vitamins and minerals (calcium and phosphate) were given to infants in the intervention group.

Comparators

The control group received human milk supplemented with vitamins and minerals (calcium and phosphate).

Outcomes

The trial reported data for our predefined short-term growth outcomes but no data was reported on long-term growth, body mass index (BMI), body composition, neurodevelopmental, and cardio-metabolic outcomes. Of all our secondary outcomes, data were available only for feeding intolerance. Additional data were provided for weight at study end.

Excluded studies

We excluded five full-text articles (three trials) from this 2018 update. Two trials used interventions that did not meet our predefined criteria (Fewtrell 2011; Makrides 1997), while the other provided data that were not usable Rönnholm 1984. Infants in this latter trial were randomised by alternate allocation to no supplementation, supplementation with protein, supplementation with fat (medium-chain triglyceride, MCT), or supplementation with both protein and fat. The authors stated that there was no apparent effect from the addition of fat alone and, therefore, combined the groups according to protein supplementation. It was impossible to extract data for the group of infants receiving only fat. See Characteristics of excluded studies for details of exclusions.

Risk of bias in included studies

Overall, we scored all items as unclear risk of bias as there was insufficient methodological detail to make a judgement. See Characteristics of included studies and the 'risk of bias' graph and summary (Figure 2; Figure 3) for details.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

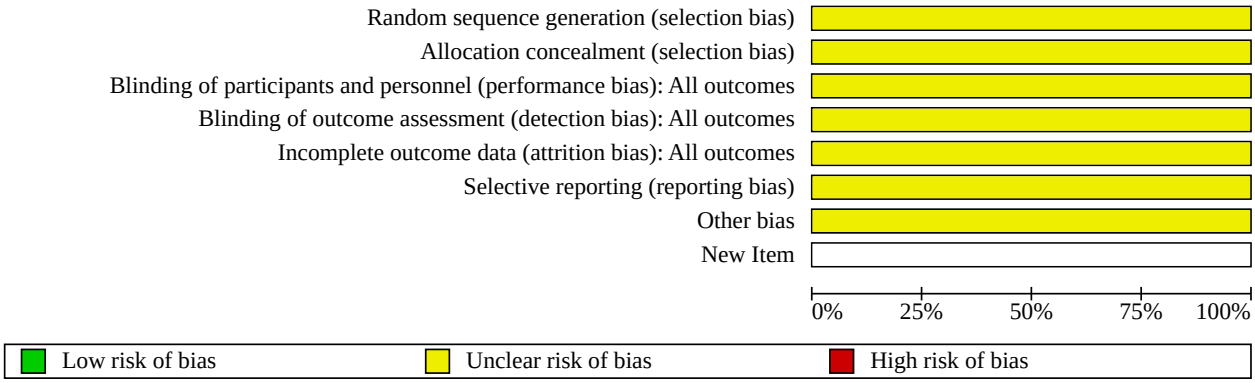
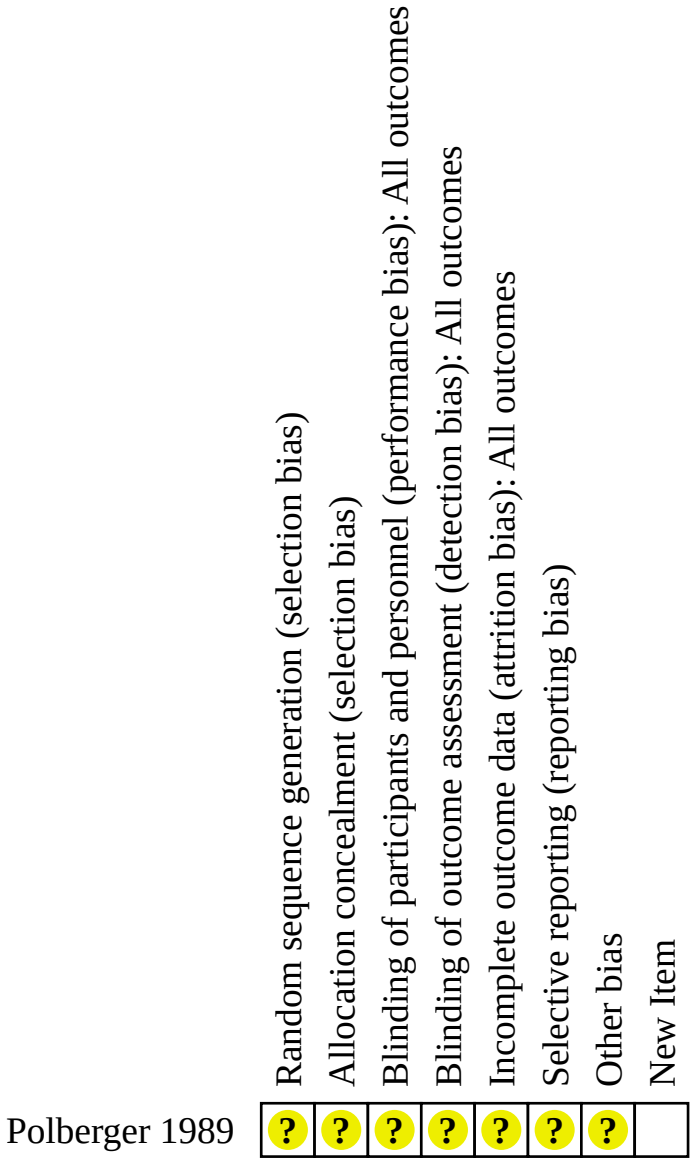


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

We judged random sequence generation and allocation concealment as unclear risk due to insufficient methodological details.

Blinding

We judged performance and detection bias as unclear risk because of lack of information on how blinding was achieved.

Incomplete outcome data

We judged attrition bias as unclear risk because the authors did not report if any differences existed between infants excluded and included in the study. The feeding groups of the excluded infants were also not clarified.

Selective reporting

We judged reporting bias as unclear risk because no details were given as to which were primary and secondary outcomes. We did

not view the protocol to ascertain whether the outcomes reported were the only ones collected.

Other potential sources of bias

We judged other potential sources of bias as unclear risk because no details were provided on how the authors resolved differences in sex distribution between the supplemented and unsupplemented groups.

Effects of interventions

See: **Summary of findings 1** Fat supplementation compared to control for promoting growth in preterm infants

1.0 Fat supplementation versus control

1.1 Growth - weight

1.1.1 Weight gain

One randomised controlled trial including 14 infants contributed data (Polberger 1989). Fat supplementation of human milk was not associated with an increase in weight gain compared with unsupplemented human milk (MD 0.6 g/kg/day, 95% CI −2.4 to 3.6; 1 RCT, n = 14 infants, very low-quality evidence). We downgraded the evidence for risk of bias as there was insufficient methodological information provided to be able to make a judgement. We also downgraded the evidence two levels for imprecision due to the very small sample size and wide confidence intervals spanning across benefits and harms.

1.1.2 Weight at the end of the study

Polberger 1989 reported the weight at the end of the study which was defined as a weight of 2200 grams or when breastfeeding was initiated. There was evidence of a clear difference in weight between the fat-supplemented and the unsupplemented groups (MD 40.0 g, 95% CI −258.6 to 338.6; 1 RCT, n = 14).

1.2 Growth - length

1.2.1 Length gain

Polberger 1989 contributed data. There was no evidence of a clear difference in length between the fat-supplemented and the unsupplemented groups (MD 0.1 cm/week, 95% CI −0.08 to 0.3; 1 RCT, n = 14, very low-quality evidence). We downgraded the evidence for risk of bias as there was insufficient methodological information provided to be able to make a judgement. We also downgraded the evidence two levels for imprecision due to the very small sample size and wide confidence intervals spanning across benefits and harms.

1.3 Growth - head circumference

1.3.1 Head circumference gain

Polberger 1989 contributed data. There was evidence of a clear difference in head growth between the fat-supplemented and the unsupplemented groups (MD 0.2 cm/week, 95% CI −0.07 to 0.4; 1 RCT, n = 14, very low-quality evidence). We downgraded the evidence for risk of bias as there was insufficient methodological information provided to be able to make a judgement. We also downgraded the evidence two levels for imprecision due to the very small sample size and wide confidence intervals spanning across benefits and harms.

1.4 Feeding intolerance

Polberger 1989 contributed data. There was no clear evidence that fat supplementation increased the risk of feeding intolerance (RR 3.0, 95% CI 0.1 to 64.3;1 RCT, n = 16 infants, very low-quality evidence). We downgraded the evidence for risk of bias as there was insufficient methodological information to make a judgement. We also downgraded two levels for imprecision due to the very small sample size, few events and wide confidence intervals.

The study did not evaluate any of our other prespecified primary or secondary outcomes including long-term growth, BMI, body composition, neurodevelopmental and cardio-metabolic outcomes.

We were unable to conduct our prespecified subgroup analysis due to insufficient data.

DISCUSSION

Summary of main results

One randomised controlled trial involving 14 preterm infants showed no evidence of an effect of fat supplementation of human milk on in-hospital rates of growth in weight, length, and head circumference. There was no clear evidence of a difference in the risk of feeding intolerance between the fat-supplemented and unsupplemented groups. No data were available for the assessment of the effects of fat supplementation on long-term growth outcomes, BMI, body composition, neurodevelopmental, and cardio-metabolic outcomes. There were limited data to assess adverse effects.

Overall completeness and applicability of evidence

The only trial included in this review had a very small sample size with methodological flaws that put it at unclear risk of bias in all the 'Risk of bias' domains (Figure 2; Figure 3). The available data were limited and incomplete as some of our outcomes of interest, including long-term growth, BMI, body composition, neurodevelopmental and cardio-metabolic outcomes, were not evaluated. Therefore, no conclusions can be drawn on the effects of fat supplementation of human milk fed to preterm infants. Additionally, for the same reasons, no conclusions can be drawn on the applicability of the evidence.

Quality of the evidence

The overall quality of evidence for all our reported outcomes was judged to be of very low-quality due to a combination of several factors. Firstly, the authors failed to report essential methodological details, including method of randomisation, blinding of study personnel, and outcome assessors. Without such information, it is difficult to adequately judge the risk of bias and quality of evidence. Secondly, the small sample size, few events, and wide confidence intervals, which included possible meaningful benefits and harms, diminished our confidence in the effect estimates.

Potential biases in the review process

We were unable to create funnel plots to assess the potential risk of publication or reporting bias as we had only one trial included in this review. We made every effort to minimise bias by conducting a systematic search of the literature. However, the

possibility of missing relevant evidence cannot be excluded. The authors' independent screening of articles and extraction of data in this review also minimised the potential for bias.

Agreements and disagreements with other studies or reviews

To our knowledge, there are no other previous systematic reviews conducted on this topic except for our previous review which included the same single randomised controlled trial published in 2000 and involving 14 preterm infants (Kuschel 2000). We reported similar findings of lack of clear differences between the fat-supplemented and unsupplemented groups with regards to short-term rates of weight gain, length gain, head growth, and feeding intolerance.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of high-quality evidence on the effects of fat supplementation of human milk in preterm infants prevents us from making recommendations for practice.

Implications for research

Given the progression to widespread use of multi-nutrient supplementation of human milk in preterm infants, we consider that further randomised trials evaluating short- and long-term growth and health outcomes in preterm infants supplemented with fat will do so in the context of multi-component fortifiers. Future trials with large sample sizes should focus on optimal dosage, delivery options, and adverse effects such as feed intolerance, necrotising enterocolitis, and diarrhoea.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Polberger 1989

Study characteristics	
Methods	Parallel randomised controlled trial in two neonatal units.
Participants	Inclusion criteria: birth weight < 1500 g, appropriate-for-gestational-age, tolerance of complete enteral feeding (170 mL/kg/day), no obvious disease or major malformations, no oxygen therapy, and informed parental consent and acceptance of a blind trial Exclusion criteria: not stated Setting: two neonatal units of the University of Lund in Malmo and Lund Timing: not stated

Polberger 1989 *(Continued)*

Interventions	1.0 g of human milk fat per 100 mL unpasteurised human milk (maternal or term banked donor) (n = 7) versus unsupplemented human milk (n = 7). Intervention ceased when the infant reached approximately 2200 g or was breastfed. All infants were supplemented with additional vitamins, calcium lactate (30 mg/kg/day) and sodium phosphate (20 mg/kg/day). From 4 weeks, 2 mg/kg/day elemental iron was given to all infants.
Outcomes	The outcomes were not specified as primary or secondary but the following were assessed: short-term growth parameters (weight, crown-heel length, occipito-frontal head circumference), intake of protein, fat, carbohydrates, energy, and electrolytes (sodium, potassium, calcium).
Notes	Conflicts of interest: no details Source of Funding: supported in part by the Swedish Medical Research Council, Grant No. B85- I'IX-06259, and Stiftelsen Saniarite This study had four arms: unsupplemented versus supplemented with protein versus supplemented with fat versus supplemented with fat and protein. The analyses of the protein and combined fat and protein arms are discussed in other reviews on multi-component and protein supplementation, respectively (Brown 2016; Kuschel 2000). Of the 34 infants enrolled in the study, 6 were withdrawn following randomisation for apnoea (n = 2), intolerance to accepting the fixed volume (n = 3) and need for intravenous therapy (n = 1).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	The study used closed envelopes without specifying if they were opaque or not.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The study was stated to be double-blinded, but who was blinded was not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not specified whether outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The missing data (i.e. from 6 infants) was less than 20%. They were excluded for the following reasons: 2 had apnoea, 3 developed feeding intolerance, and 1 needed intravenous therapy. However, the authors did not report whether there were any differences between infants excluded and included in the study.
Selective reporting (reporting bias)	Unclear risk	No details were given as to which were primary and secondary outcomes, and no protocol was viewed to clarify whether the outcomes reported were the only ones collected.
Other bias	Unclear risk	The authors stated 'there was a difference in sex distribution between the groups and later analyses confirmed that this difference had no implications on the results'. However, no further details were provided as to how this conclusion was reached.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fewtrell 2011	Irrelevant intervention
Lauterbach 2015	A commentary of a trial with irrelevant intervention
Makrides 1997	Fat supplementation of maternal diet of lactating mothers
Rönnholm 1984	Unable to extract data for infants supplemented with fat alone

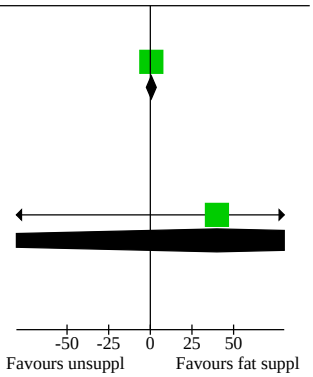
DATA AND ANALYSES

Comparison 1. Fat supplementation vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Growth - weight	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Weight gain (g/kg/day)	1	14	Mean Difference (IV, Fixed, 95% CI)	0.60 [-2.36, 3.56]
1.1.2 Weight at end of study (g)	1	14	Mean Difference (IV, Fixed, 95% CI)	40.00 [-258.62, 338.62]
1.2 Growth - length	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Length gain (cm/week)	1	14	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.08, 0.28]
1.3 Growth - head circumference	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 Head growth (cm/week)	1	14	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.07, 0.37]
1.4 Feeding intolerance	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

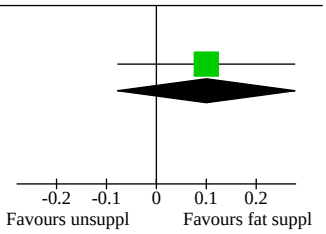
Analysis 1.1. Comparison 1: Fat supplementation vs control, Outcome 1: Growth - weight

Study or Subgroup	Fat suppl Mean	SD	Total	Unsuppl Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Weight gain (g/kg/day)								
Polberger 1989	15.9	2.4	7	15.3	3.2	7	100.0%	0.60 [-2.36 , 3.56]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.60 [-2.36 , 3.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.40 (P = 0.69)								
1.1.2 Weight at end of study (g)								
Polberger 1989	2110	200	7	2070	350	7	100.0%	40.00 [-258.62 , 338.62]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**40.00 [-258.62 , 338.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.79)								



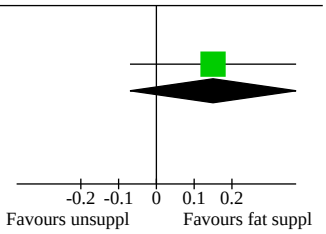
Analysis 1.2. Comparison 1: Fat supplementation vs control, Outcome 2: Growth - length

Study or Subgroup	Fat suppl Mean	SD	Total	Unsuppl Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Length gain (cm/week)								
Polberger 1989	0.93	0.17	7	0.83	0.17	7	100.0%	0.10 [-0.08 , 0.28]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.10 [-0.08 , 0.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.10 (P = 0.27)								



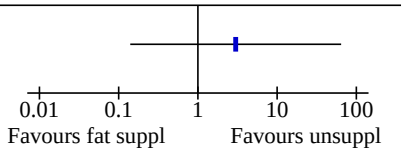
Analysis 1.3. Comparison 1: Fat supplementation vs control, Outcome 3: Growth - head circumference

Study or Subgroup	Fat suppl Mean	SD	Total	Unsuppl Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 Head growth (cm/week)								
Polberger 1989	1.09	0.16	7	0.94	0.25	7	100.0%	0.15 [-0.07 , 0.37]
Subtotal (95% CI)			**7**			**7**	**100.0%**	**0.15 [-0.07 , 0.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								



Analysis 1.4. Comparison 1: Fat supplementation vs control, Outcome 4: Feeding intolerance

Study or Subgroup	Fat suppl Events	Fat suppl Total	Unsuppl Events	Unsuppl Total	Risk Ratio M-H, Fixed, 95% CI
Polberger 1989 (1)	1	8	0	8	3.00 [0.14 , 64.26]
Test for subgroup differences: Not applicable					



Footnotes

(1) These figures are from the previous review published in 1999 after consultations with the authors of the publication.

APPENDICES

Appendix 1. Search methods 2020 update

MEDLINE via PubMed:

1	lipids[MeSH] OR Fatty Acids, Omega-3[MeSH] OR Fish Oils [MeSH]
2	fat[tiab] OR lipid*[tiab] OR "medium chain triglycerides"[tiab] OR MCT[tiab] OR microlipid[tiab] OR “Arachidonic Acid”[tiab] OR “Docosahexaenoic acid”[tiab] OR “Omega-3 Fatty acids”[tiab] OR “Omega-6 fatty acids”[tiab] OR “N-3 Fatty Acid”[tiab] OR “N-6 Fatty Acid” OR LCPUFA OR linolenate
3	(Fish[tiab] OR "Cod Liver"[tiab] OR corn[tiab] OR safflower[tiab] OR soy[tiab] OR coconut[tiab]) AND Oil*[tiab]
4	(PUFA[tiab] OR Fatty Acid*[tiab]) OR (Polyunsaturated[tiab] AND n-3[tiab])
5	(alpha-Linolenic OR Docosahexaenoic OR Docosahexenoic OR Docosahexaenoate OR Eicosapentaenoic OR Eicosapentanoic OR Timnodonic OR Icosapentaenoic OR Fatty Omega-3) AND Acid*
6	1 OR 2 OR 3 OR 4 OR 5
7	Milk, Human[MeSH]
8	breastmilk*[tiab]
9	((human[tiab] OR breast[tiab] OR expressed[tiab] OR mother*[tiab] OR maternal[tiab] OR donor*[tiab]) AND milk*[tiab])
10	7 OR 8 OR 9
11	((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
12	6 AND 10 AND 11

Cochrane Library:

1	MESH DESCRIPTOR Fish Oils EXPLODE ALL AND CENTRAL:TARGET
2	MESH DESCRIPTOR Fatty Acids, Omega-3 EXPLODE ALL AND CENTRAL:TARGET
3	MESH DESCRIPTOR Fatty Acids, Omega-6 EXPLODE ALL AND CENTRAL:TARGET
4	MESH DESCRIPTOR Eicosanoic Acids EXPLODE ALL AND CENTRAL:TARGET
5	MESH DESCRIPTOR Docosahexaenoic Acids EXPLODE ALL AND CENTRAL:TARGET
6	MESH DESCRIPTOR Linoleic Acid EXPLODE ALL AND CENTRAL:TARGET
7	(fat or lipid* or 'medium chain triglycerides' or MCT or microlipid or LCPUFA or linolenate) : TI,AB AND CENTRAL:TARGET
8	((Fish or 'Cod Liver' or corn or safflower or soy or coconut) NEXT Oil*) :TI,AB,KW AND CENTRAL:TARGET
9	(('alpha linolenic' or arachidonic or docosahexaenoic or docosahexenoic or docosahexaenoate or eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic or 'fatty omega-3' or 'Omega-3 Fatty' or 'Omega-6 fatty'or 'N-3 Fatty' or 'N-6 Fatty') NEXT acid*):TI,AB,KW AND CENTRAL:TARGET
10	((PUFA or Fatty Acid* or Polyunsaturated) NEXT n-3):TI,AB,KW AND CENTRAL:TARGET
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	MESH DESCRIPTOR Milk, Human EXPLODE ALL AND CENTRAL:TARGET
13	((human OR breast OR expressed) NEAR2 milk*):TI,AB,KW AND CENTRAL:TARGET
14	((mother* or maternal or donor*) NEAR2 milk*): TI,AB,KW AND CENTRAL:TARGET
15	#12 OR #13 OR #14
16	(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) AND CENTRAL:TARGET
17	#11 AND #15 AND #16

Appendix 2. Risk of bias tool

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we categorised the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we categorised the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk.

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we categorised the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk, high risk, or unclear risk for participants; and
- low risk, high risk, or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we categorised the methods used to blind outcome assessment. Blinding was assessed separately for different outcomes or class of outcomes. We categorised the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion, where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorised the methods as:

- low risk (< 20% missing data);
- high risk (≥ 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we compared prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we contacted study authors to gain access to the study protocol. We assessed the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk.

If needed, we explored the impact of the level of bias through undertaking sensitivity analyses.

Appendix 3. Previous search methods

MEDLINE via PubMed:

1	lipids[MeSH] OR Fatty Acids, Omega-3[MeSH] OR Fish Oils [MeSH]
2	fat[tiab] OR lipid*[tiab] OR "medium chain triglycerides"[tiab] OR MCT[tiab] OR microlipid[tiab] OR “Arachidonic Acid”[tiab] OR “Docosahexaenoic acid”[tiab] OR “Omega-3 Fatty acids”[tiab] OR “Omega-6 fatty acids”[tiab] OR “N-3 Fatty Acid”[tiab] OR “N-6 Fatty Acid” OR LCPUFA OR linolenate
3	(Fish[tiab] OR "Cod Liver"[tiab] OR corn[tiab] OR safflower[tiab] OR soy[tiab] OR coconut[tiab]) AND Oil*[tiab]
4	(PUFA[tiab] OR Fatty Acid*[tiab]) OR (Polyunsaturated[tiab] AND n-3[tiab])
5	(alpha-Linolenic OR Docosahexaenoic OR Docosahexenoic OR Docosahexaenoate OR Eicosapentaenoic OR Eicosapentanoic OR Timnodonic OR Icosapentaenoic OR Fatty Omega-3) AND Acid*
6	1 OR 2 OR 3 OR 4 OR 5
7	Milk, Human[MeSH]
8	breastmilk*[tiab]
9	((human[tiab] OR breast[tiab] OR expressed[tiab] OR mother*[tiab] OR maternal[tiab] OR donor*[tiab]) AND milk*[tiab])
10	7 OR 8 OR 9
11	((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))
12	6 AND 10 AND 11

Embase:

1	exp lipid/
2	exp omega 3 fatty acid/
3	exp fish oil/
4	exp medium chain triacylglycerol/
5	exp arachidonic acid/
6	exp docosahexaenoic acid/
7	exp omega 6 fatty acid/
8	exp linolenic acid/
9	(fat or lipid* or 'medium chain triglycerides' or MCT or microlipid or LCPUFA or linolenate).ti,ab.
10	((Fish or 'Cod Liver' or corn or safflower or soy or coconut) adj Oil*).ti,ab.

(Continued)

11	(('alpha linolenic' or arachidonic or docosahexaenoic or docosahexenoic or docosahexaenoate or eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic or 'fatty omega-3' or 'Omega-3 Fatty' or 'Omega-6 fatty'or 'N-3 Fatty' or 'N-6 Fatty') adj acid*).ti,ab.
12	((PUFA or Fatty Acid* or Polyunsaturated) adj n-3).ti,ab.
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14	exp breast milk/
15	((human or breast or expressed) adj milk$).ti,ab.
16	((mother$ or maternal or donor$) adj milk$).ti,ab.
17	14 or 15 or 16
18	(infan* or newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
19	exp infant/
20	18 or 19
21	(human not animal).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
22	(randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
23	20 and 21 and 22
24	13 and 17 and 23

CINAHL:

S1	(MH "Fatty Acids, Omega-3+") OR (MH "Fatty Acids, Omega-6+") OR (MH "Fatty Acids, Unsaturated+")
S2	TI (((Fish or 'Cod Liver' or corn or safflower or soy or coconut) N2 Oil*)) OR AB (((Fish or 'Cod Liver' or corn or safflower or soy or coconut) N2 Oil*))
S3	TI ((fat or lipid* or 'medium chain triglycerides' or MCT or microlipid or LCPUFA or linolenate)) OR AB ((fat or lipid* or 'medium chain triglycerides' or MCT or microlipid or LCPUFA or linolenate))
S4	TI ((('alpha linolenic' or arachidonic or docosahexaenoic or docosahexenoic or docosahexaenoate or eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic or 'fatty omega-3' or 'Omega-3 Fatty' or 'Omega-6 fatty'or 'N-3 Fatty' or 'N-6 Fatty') N2 acid*)) OR AB ((('alpha linolenic' or arachidonic or docosahexaenoic or docosahexenoic or docosahexaenoate or eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic or 'fatty omega-3' or 'Omega-3 Fatty' or 'Omega-6 fatty'or 'N-3 Fatty' or 'N-6 Fatty') N2 acid*))

(Continued)

S5	TI (((PUFA or Fatty Acid* or Polyunsaturated) N2 n-3)) OR AB (((PUFA or Fatty Acid* or Polyunsaturated) N2 n-3))
S6	S1 OR S2 OR S3 OR S4 OR S5
S7	MH "Milk, Human+" OR TI (((human or breast or expressed) N2 milk*)) OR AB (((human or breast or expressed) N2 milk*)) OR TI (((mother* or maternal or donor*) N2 milk*)) OR AB (((mother* or maternal or donor*) N2 milk*)) OR TI "breastmilk" OR AB "breastmilk"
S8	(infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
S9	S6 AND S7 AND S8

Cochrane Library:

1	MESH DESCRIPTOR Fish Oils EXPLODE ALL AND CENTRAL:TARGET
2	MESH DESCRIPTOR Fatty Acids, Omega-3 EXPLODE ALL AND CENTRAL:TARGET
3	MESH DESCRIPTOR Fatty Acids, Omega-6 EXPLODE ALL AND CENTRAL:TARGET
4	MESH DESCRIPTOR Eicosanoic Acids EXPLODE ALL AND CENTRAL:TARGET
5	MESH DESCRIPTOR Docosahexaenoic Acids EXPLODE ALL AND CENTRAL:TARGET
6	MESH DESCRIPTOR Linoleic Acid EXPLODE ALL AND CENTRAL:TARGET
7	(fat or lipid* or 'medium chain triglycerides' or MCT or microlipid or LCPUFA or linolenate) : TI,AB AND CENTRAL:TARGET
8	((Fish or 'Cod Liver' or corn or safflower or soy or coconut) NEXT Oil*) :TI,AB,KW AND CENTRAL:TARGET
9	(('alpha linolenic' or arachidonic or docosahexaenoic or docosahexenoic or docosahexaenoate or eicosapentaenoic or eicosapentanoic or timnodonic or icosapentaenoic or 'fatty omega-3' or 'Omega-3 Fatty' or 'Omega-6 fatty'or 'N-3 Fatty' or 'N-6 Fatty') NEXT acid*):TI,AB,KW AND CENTRAL:TARGET
10	((PUFA or Fatty Acid* or Polyunsaturated) NEXT n-3):TI,AB,KW AND CENTRAL:TARGET
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	MESH DESCRIPTOR Milk, Human EXPLODE ALL AND CENTRAL:TARGET
13	((human OR breast OR expressed) NEAR2 milk*):TI,AB,KW AND CENTRAL:TARGET
14	((mother* or maternal or donor*) NEAR2 milk*): TI,AB,KW AND CENTRAL:TARGET
15	#12 OR #13 OR #14

(Continued)

16	(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) AND CENTRAL:TARGET
17	#11 AND #15 AND #16

WHAT'S NEW

Date	Event	Description
20 October 2020	Amended	Abstract results amended to better align with summary of findings table. In future, this review will no longer be updated, as it will be superseded by Cochrane Review Multi-nutrient fortification of human milk for preterm infants (Brown 2020).

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 3, 1999

Date	Event	Description
29 June 2020	New search has been performed	• We updated the search for eligible studies to August 2019. • We found no new randomised controlled trials eligible for inclusion in this review.
29 June 2020	New citation required but conclusions have not changed	A supplementary search was carried out in August 2019. No new studies were identified. The main conclusions of the original review remain unchanged.
9 February 2018	New citation required but conclusions have not changed	A supplementary search was carried out in February 2018. No new studies were identified. The main conclusions of the original review remain unchanged.
23 January 2018	New search has been performed	• We updated the search for eligible studies to February 2018. • We found no new randomised controlled trials eligible for inclusion in this review. • We included body mass index and measures of body composition in the growth parameters of the primary outcome. We also included new secondary outcome measures: long-term measures of cardio-metabolic health (such as insulin resistance, obesity, diabetes and hypertension). These outcomes were aligned with those of the Cochrane Review Multi-Nutrient Fortification of Human Milk for Preterm Infants Brown 2016. • We incorporated the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of evidence.
10 April 2002	New search has been performed	This is an update of the existing review of "Fat supplementation of human milk for promoting growth in preterm infants", The Cochrane Library, Issue 3, 1999.

Date	Event	Description
		No new trials were located in the search done in April 2002, and as a result, no substantive changes were made in the review. There was no change to the conclusion that there is insufficient evidence evaluating the supplementation of human milk with fat in preterm infants to make recommendations for practice.
13 December 1999	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

For the 2018 update:

Emma Amissah assessed study eligibility, performed data extraction and 'Risk of bias' assessment of included studies, analysed data, interpreted results of the analysis, and updated the review. She wrote all drafts and addressed comments from co-authors.

Julie Brown assessed study eligibility, performed data extraction and 'Risk of bias' assessment of included studies, assisted in the interpretation of analyses, and provided comments on drafts.

Jane Harding answered queries on trial eligibility, assisted in the interpretation of analyses, and provided comments on all drafts of the review.

All authors read and approved the final version of the review.

For the 2020 update:

Only the search was updated, with no new trials found. The search was screened by Cochrane Neonatal in consultation with Jane Harding. All previous author contributions remain the same, as the text of the review remains unchanged.

DECLARATIONS OF INTEREST

EA receives a scholarship in the form of a stipend from the University of Auckland as a PhD student.

JB is currently employed by a medical writing company. The preparation of this review took place prior to this employment and her current work is not related to the topic of this review.

JH has partial salary support from research grants from the Health Research Council of New Zealand. The Council has no role in the production of this review. An undirected research grant is pending from Biomed Ltd, Auckland, New Zealand. This company makes dextrose gel.

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- Vermont Oxford Network, USA

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- The Gerber Foundation, USA

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2018 update:

The original protocol was published in 1997, and was the basis of the last version of this review written in 2000. The 2018 update aligned the review outcomes with those of the Cochrane Review, Multi-nutrient fortification of human milk for preterm infants (Brown 2016). We added body mass index and measures of body composition as part of growth parameters of the primary outcome. We also included new secondary outcome measures: long-term measures of cardio-metabolic health (such as insulin resistance, obesity, diabetes, and hypertension) We also added the 'Summary of Findings' tables and GRADE recommendations, which were not included in the original protocol.

For the 2020 update:

As of July 2019, Cochrane Neonatal no longer searches Embase for its reviews. RCTs and controlled clinical trials (CCTs) from Embase are added to the Cochrane Central Register of Controlled Trials (CENTRAL) via a robust process (see How CENTRAL is created). Cochrane Neonatal has validated their searches to ensure that relevant Embase records are found while searching CENTRAL.

Also starting in July 2019, Cochrane Neonatal no longer searches for RCTs and CCTs on the following platforms: ClinicalTrials.gov or from The World Health Organization's International Clinical Trials Registry Platform (ICTRP), as records from both platforms are added to CENTRAL on a monthly basis (see How CENTRAL is created). Comprehensive search strategies are executed in CENTRAL to retrieve relevant records. The ISRCTN (at www.isrctn.com/, formerly Controlled-trials.com), is searched separately.

We did not search CINAHL for this update. The 2018 search methods are listed in Appendix 3.

INDEX TERMS

Medical Subject Headings (MeSH)

Dietary Fats [*administration & dosage]; *Dietary Supplements; *Infant Nutritional Physiological Phenomena; Infant, Premature [*growth & development]; *Milk, Human

MeSH check words

Humans; Infant, Newborn