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Lipid emulsions for parenterally fed term and late preterm infants (Review)

Kapoor V, Malviya MN, Soll R

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[Intervention Review]

Lipid emulsions for parenterally fed term and late preterm infants

Vishal Kapoor¹, Manoj N Malviya², Roger Soll³

¹Department of Paediatrics, Queensland Children's Hospital, Brisbane, Australia. ²Neonatal Intensive Care Unit, Khoulou Hospital, Muscat, Oman. ³Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Larner College of Medicine at the University of Vermont, Burlington, Vermont, USA

Contact address: Roger Soll, Division of Neonatal-Perinatal Medicine, Department of Pediatrics, Larner College of Medicine at the University of Vermont, 111 Colchester Avenue, Burlington, Vermont, 05401, USA. roger.soll@uvmhealth.org.

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ABSTRACT

Background

Lipid emulsions (LE) form a vital component of infant nutrition for critically ill, late preterm or term infants, particularly for those with gastrointestinal failure. Conventionally used soybean oil-based LE (S-LE) have high polyunsaturated fatty acid (PUFA) content and phytosterols, which may contribute to adverse effects including parenteral nutrition-associated liver disease (PNALD).

Objectives

To compare the safety and efficacy of all LE for parenteral nutrition (PN) in term and late preterm infants (between 34 weeks' gestation and 36 weeks' and six days' gestation) with or without surgical conditions or PNALD within first six months of life, using all possible direct comparisons.

Search methods

We used the standard search strategy of Cochrane Neonatal to search the Cochrane Central Register of Controlled Trials (CENTRAL 2018, Issue 5), MEDLINE (1946 to 18 June 2018), Embase (1974 to 18 June 2018), CINAHL (1982 to 18 June 2018), MIDRIS (1971 to 31 May 2018), conference proceedings, trial registries ([ClinicalTrials.gov](https://clinicaltrials.gov) and the WHO's [Trials Registry](https://trialsregistry.org)), and the reference lists of retrieved articles for randomised controlled trials and quasi-randomised trials.

Selection criteria

Randomised or quasi-randomised controlled studies in term and late preterm infants, with or without surgical conditions or PNALD.

Data collection and analysis

Data collection and analysis conformed to the methods of Cochrane Neonatal. We used the GRADE approach to assess the quality of evidence for important outcomes in addition to reporting the conventional statistical significance of results.

Main results

The review included nine randomised studies (n = 273). LE were classified in three broad groups: 1. all fish oil-containing LE including pure fish oil (F-LE) and multisource LE (e.g. medium-chain triglycerides (MCT)-olive-fish-soybean oil-LE (MOFS-LE), MCT-fish-soy oil-LE (MFS-LE) and olive-fish-soy-LE (OFS-LE)); 2. conventional pure S-LE; 3. alternative-LE (e.g. MCT-soy-LE (MS-LE), olive-soy-LE (OS-LE) and borage oil-based LE).

We considered four broad comparisons: 1. all fish oil LE versus non-fish oil LE (6 studies; n = 182); 2. fish oil LE versus another fish oil LE (0 studies); 3. alternative-LE versus S-LE (3 studies; n = 91); 4. alternative-LE versus another alternative-LE (0 studies) in term and late preterm

infants (0 studies), term and late preterm infants with surgical conditions (7 studies; $n = 233$) and term and late preterm infants with PNALD/cholestasis (2 studies; $n = 40$).

PNALD/cholestasis was defined as conjugated bilirubin (Cbil) 2 mg/dL or greater and resolution of PNALD/cholestasis as Cbil less than 2 mg/dL. We put no restriction on timing of PNALD detection. There was heterogeneity in definitions and time points for detecting PNALD in the included studies.

We found one study each in surgical infants and in infants with cholestasis, showing no evidence of difference in incidence or resolution of PNALD/cholestasis (Cbil cut-off: 2 mg/dL) with use of fish oil-containing LE compared to S-LE.

We considered an outcome allowing for any definition of PNALD (different Cbil cut-off levels). In infants with surgical conditions and no pre-existing PNALD, meta-analysis showed no difference in the incidence of PNALD/cholestasis (any definition) with use of fish oil-containing LE compared to S-LE (typical risk ratio (RR) 1.20, 95% confidence interval (CI) 0.38 to 3.76; typical risk difference (RD) 0.03, 95% CI -0.14 to 0.20; 2 studies; $n = 68$; low-quality evidence). In infants with PNALD/cholestasis (any definition), use of fish oil-LEs was associated with significantly less cholestasis compared to the S-LE group (typical risk ratio (RR) 0.54, 95% confidence interval (CI) 0.32 to 0.91; typical risk difference (RD) -0.39, 95% CI -0.65 to -0.12; number needed to treat for additional beneficial outcome (NNTB) 3, 95% CI 2 to 9; 2 studies; $n = 40$; very low-quality evidence). This outcome had very low number of participants from two small studies with differences in study methodology and early termination in one study, which increased uncertainty about the effect estimates.

One study in infants with cholestasis reported significantly better weight gain with a pure fish oil LE compared to a 10% S-LE (45 g/week, 95% CI 15.0 to 75.0; $n = 16$; very low-quality evidence). There were no significant differences in growth parameters in studies with surgical populations.

For the secondary outcomes, in infants with cholestasis, one study ($n = 24$) reported significantly lower conjugated bilirubin levels but higher gamma glutamyl transferase levels with MOFS-LE (SMOFlipid) versus S-LE (Intralipid) and another study ($n = 16$), which was terminated early, reported significantly higher rates of rise in alanine aminotransferase (ALT) and conjugated bilirubin levels in the S-LE group compared to pure F-LE (Omegaven).

In surgical infants, two studies each reported on hypertriglyceridaemia and Cbil levels with one study in each outcome showing significant benefit with use of a F-LE and the other study showing no difference between the groups. Meta-analysis was not performed for either of these outcomes as there were only two studies showing conflicting results with high heterogeneity between the studies.

There was no evidence of differences in death, sepsis, alkaline phosphatase and ALT levels in infants with surgical conditions or cholestasis (very low-quality evidence).

One study reported neurodevelopmental outcomes at six and 24 months in infants with surgical conditions ($n = 11$) with no evidence of difference with use of pure F-LE versus S-LE. Another study in infants with cholestasis ($n = 16$) reported no difference in head growth velocity between pure F-LE versus S-LE.

GRADE quality of evidence ranged from low to very low as the included studies were small single-centre studies. Three of the six studies that contributed data to the review were terminated early for various reasons.

Authors' conclusions

Based on the current review, there is insufficient data from randomised studies to determine with any certainty, the potential benefit of any LE including fish oil-containing LEs over another LE, for prevention or resolution of PNALD/cholestasis or any other outcomes in term and late preterm infants with underlying surgical conditions or cholestasis. There were no studies in infants without surgical conditions or cholestasis.

Further research is required to establish role of fish oil or lipids from other sources in LEs to improve PNALD/cholestasis, and other clinical outcomes in parenterally fed term and late preterm infants.

PLAIN LANGUAGE SUMMARY

Systematic review of lipid emulsions for intravenous nutrition in term and late preterm infants.

Review question: which lipid (fat) emulsions (LE) have the best outcomes in term and late preterm infants (greater than 34 weeks' gestation (time between becoming pregnant and giving birth)) with or without pre-existing liver disease and surgical conditions?

Background: infants who need nutrition through an intravenous line (tube into a vein) have been conventionally given pure soybean oil-based lipid emulsions. However, high polyunsaturated fatty acid (PUFA) content and phytosterols in pure soybean oil-based LEs may be harmful and may contribute to parenteral nutrition-associated liver disease (PNALD) and other side effects. The newer LEs from other lipid sources including fish oil may potentially improve clinical outcomes in term and late preterm infants by decreasing PUFA content and providing specific benefits.

Study characteristics: the review authors searched the medical literature and identified nine eligible studies (including 273 preterm infants). Evidence is up to date as of 18 June 2018.

Key findings: there is a paucity of research in this field with a limited number of studies, many of which were terminated early. There is very low quality and limited evidence to suggest that fish oil-based LE may improve some liver disease-related outcomes in infants with pre-existing liver disease. However, this evidence was based on very limited number of participants from two small studies, one of which was terminated early, so that no certain conclusions could be drawn. There was no evidence of benefit in other clinically important outcomes, for example, sepsis, rate of growth or death with any LE including fish oil-LE over another LE in term and late preterm infants with surgical conditions or liver disease. We found no studies in infants without surgical conditions or pre-existing liver disease.

Conclusions: we found that in the population of term and late preterm infants (greater than 34 weeks' gestation) with pre-existing liver disease or surgical conditions, there is currently insufficient evidence from well-designed studies to determine beneficial effects of any LE including the fish oil-containing LEs over another LE for prevention or resolution of liver disease or other clinically important outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Fish oil LE compared to non-fish oil LE in infants with surgical conditions for parenterally fed term and late preterm infants

Fish oil LE compared to non-fish oil LE in infants with surgical conditions for parenterally fed term and late preterm infants

Patient or population: parenterally fed term and late preterm infants with surgical conditions

Settings: neonatal intensive care units

Intervention: fish oil LE

Comparison: non-fish oil LE

Outcomes	Illustrative comparative risks* (95% CI)		Relative ef- fect (95% CI)	No of partici- pants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Non-fish oil LE	Fish oil LE				
PNALD/cholesta- sis (conjugated bilirubin ≥ 2 mg/ dL) Pure F-LE vs S-LE Follow-up: mean 5 weeks	Study population		RR 1.11 (0.08 to 15.28)	19 (1 studies)	⊕⊕⊕⊕ Very low ^{a,b,c}	Only 1 study was includ- ed in this outcome. This study was terminated early due to low inci- dence of cholestasis over 2 years.
	100 per 1000	111 per 1000 (8 to 1000)				
PNALD/cholesta- sis (any defini- tion)	Study population		RR 1.2 (0.38 to 3.76)	68 (2 studies)	⊕⊕⊕⊕ Low ^{a,b}	—
	135 per 1000	162 per 1000 (51 to 508)				
	Moderate					
	124 per 1000	149 per 1000 (47 to 466)				
Culture-positive sepsis	Study population		RR 1.05 (0.47 to 2.34)	51 (2 studies)	⊕⊕⊕⊕ Very low ^{a,b,d}	—

	400 per 1000	420 per 1000 (188 to 936)				
Hypertriglyceridaemia (definitions varied from > 250 mg/dL to > 300 mg/dL)	Study 1: pure F-LE vs S-LE (n = 19)		No summary estimate	68 (2 studies)	See comment	This outcome had high between-study heterogeneity (81%) with only 2 studies in outcome and 1 of the studies was terminated early. We did not perform meta-analysis and provided the estimates from both studies separately.
	Study population: 1 study showed no hypertriglyceridaemia events (RR not estimable)					
	0 per 1000	0 per 1000				
	Study 2: MOFS-LE vs MS-LE (n = 49)					
	Study population: 1 study showed decrease in hypertriglyceridaemia RR 0.25 (0.06 to 1.01) RD -0.28 (-0.50 to -0.06)					
	90 per 1000	22 per 1000 (5 to 90)				
Conjugated bilirubin levels	—	Range of values in 2 studies: The mean conjugated bilirubin levels (µmol/L) in the fish oil LE group was 33.52 lower (50.60 to 16.44 lower) in 1 study (MOFS-LE vs S-LE) The other study did not show any difference with the mean conjugated bilirubin (µmol/L) in the fish oil LE group was 0.0 lower (11.30 lower to 11.30 higher)	No summary estimate	38 (2 studies)	See comment	Only 1 study in this outcome showed highly significant reduction in conjugated bilirubin values with the other study showing no difference. There were only 2 studies in this outcome with high heterogeneity of 90% between studies so meta-analysis was not performed. The study showing significant effect was at high risk of bias. The other study was terminated early.
ALP levels	—	The mean ALP levels (IU/L) in the intervention groups was 56.91 lower (114.7 lower to 0.87 higher)	—	38 (2 studies)	⊕⊕⊕⊕ Low ^{b,e}	—

Death before discharge	See comment	See comment	Not estimable	68 (2)	See comment	No events in either group.
Neurodevelopmental outcome (6 and 24 months)	—	Study reported no significant differences in non-parametric statistics	—	10 (1 study)	See comment	Only around half of the infants had neurodevelopmental follow-up in this small study limited by early termination.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

ALP: alkaline phosphatase; **CI:** confidence interval; **F-LE:** fish oil-containing lipid emulsion; **LE:** lipid emulsion; **MOFS-LE:** medium-chain triglyceride-olive-fish-soybean oil lipid emulsion; **MS-LE:** medium-chain triglyceride-soybean oil lipid emulsion; **PNALD:** parenteral nutrition-associated liver disease; **RD:** risk difference; **RR:** risk ratio; **S-LE:** soybean oil-based lipid emulsions.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level as the 95% confidence interval included null effect and and RR of 0.75 or 1.25 or (or the limit of appreciable benefit or harm by author consensus).

^bDowngraded by one level as optimal information size was not reached.

^cIt is not recommended to downgrade evidence on basis of a single study in an outcome as per GRADE published guidelines; however, this was a very limited sample (review author consensus) therefore the evidence was downgraded by one level.

^dDowngraded by one level as one of the studies was stopped early and contributed greater than 20% data or was the only study in the outcome.

^eOne of the studies had high risk of bias.

Summary of findings 2. Fish oil LE compared to non-fish oil LE in infants with cholestasis for parenterally fed term and late preterm infants

Fish oil LE compared to non-fish oil LE in infants with cholestasis for parenterally fed term and late preterm infants

Patient or population: parenterally fed term and late preterm infants

Settings: neonatal intensive care units

Intervention: fish oil LE

Comparison: non-fish oil LE in infants with cholestasis

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
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	Assumed risk	Corresponding risk				
	Non-fish oil LE	Fish oil LE				
PNALD/cholestasis (any definition) MOFS-LE vs S-LE Pure F-LE vs S-LE Follow-up: mean 2–4 months	Study population		RR 0.54 (0.32 to 0.91)	40 (2 studies)	⊕⊕⊕⊕ Very low ^{b,c,d}	1 trial was stopped after interim analysis. This trial used 10% Intralipid emulsion.
	800 per 1000	432 per 1000				
	continued to have cholestasis (80% rate in non-fish oil LE)	had cholestasis (256 to 728)				
Resolution of PNALD/cholestasis (conjugated bilirubin less than 2 mg/dL) Pure F-LE vs S-LE Follow-up: mean 2–4 months	Study population		RR 5.6 (0.34 to 93.35)	16 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c,e}	This study used 10% Intralipid
	0 per 1000 (baseline rate)	0 per 1000				
	50 per 1000 (if 5% infants with cholestasis improve with non-fish LE)	280 per 1000 improve with fish oil emulsion (17 to 1000)				
Growth rate (g/week) Pure F-LE vs S-LE		MD 45 g/week higher (15.00 higher to 75.00 higher)		16 (1 study)	⊕⊕⊕⊕ Very low ^{b,c,e}	
Any sepsis (clinical or culture positive (or both)) MOFS-LE vs S-LE Pure F-LE vs S-LE	Study population		RR 1.21 (0.5 to 2.92)	40 (2 studies)	⊕⊕⊕⊕ Very low ^{a,b,c}	
	300 per 1000	363 per 1000 (150 to 876)				
Hypertriglyceridaemia	Study population		RR 0.79 (0.3 to 2.09)	24 (1 study)	⊕⊕⊕⊕ Very low ^{a,b,e}	
	462 per 1000	365 per 1000 (138 to 965)				
Conjugated bilirubin levels		The mean conjugated bilirubin levels (μmol/L) in the intervention groups was 47 lower (71.65 to 22.35 lower)		24 (1 study)	⊕⊕⊕⊕ Low ^{b,e}	

ALP levels (IU/L)		The mean ALP levels (IU/L) in the intervention groups was 119 lower (240.01 lower to 2.01 higher)	24 (1 study)	⊕⊕○○ Low ^{b,e}	
Rate of change of conjugated bilirubin		The mean rate of change (increase in conjugated bilirubin) μmol/L/ week in the intervention group was 12.9 lower (23.69 to 2.11 lower)	16 (1 study)	⊕○○○ Very low ^{b,c,e}	
Death before discharge	Study population		RR 0.24 (0.03 to 1.87)	40 (2 studies)	⊕○○○ Very low ^{a,b,c}
	150 per 1000	36 per 1000 (4 to 281)			
	Moderate				
	181 per 1000	43 per 1000 (5 to 338)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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).

ALP: alkaline phosphatase; **CI:** confidence interval; **F-LE:** fish oil-containing lipid emulsion; **LE:** lipid emulsion; **MOFS-LE:** medium-chain triglyceride-olive-fish-soybean oil lipid emulsion; **PNALD:** parenteral nutrition-associated liver disease; **RCT:** randomised controlled trial; **RR:** risk ratio; **S-LE:** soybean oil-based lipid emulsions.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

^aDowngraded by one level as the confidence intervals include null effect and RR of 0.75 or 1.25 or (or the limit of appreciable benefit or harm by author consensus).

^bDowngraded by one level as the optimal information size was not reached.

^cDowngraded by one level as one of the studies was stopped early and contributed greater than 20% data or was the only study in the outcome.

^dDowngraded by one level by author consensus as the two studies in this outcome used different cut-offs for conjugated bilirubin.

^eIt is not recommended to downgrade evidence if there is only a single study in an outcome (as per GRADE published guidelines); however, this was a very limited sample size. Therefore the evidence was further downgraded for this outcome (author consensus). This downgrading would not have applied if this was a large randomised study.

BACKGROUND

Description of the condition

Maintaining adequate growth of critically ill infants is challenging (Ehrenkranz 2000; Hay 2008). Complications in critically ill, late preterm or term infants (particularly those with congenital or acquired disease causing gastrointestinal failure) make routine enteral feeding problematic, and at times impossible. These infants do not receive enough protein and energy to achieve adequate growth (Hay 2008). Frequently, they require total parenteral nutrition (TPN) or partial parenteral nutrition (PPN) to provide all or part of their caloric requirements. Lipid emulsions (LE) have been a vital component of parenteral nutrition (PN) in critically ill infants since their introduction in the 1960s. Lipids are an attractive energy source because of their high-density energy and their supply of essential fatty acids (EFA) necessary for central nervous system development (Vlaardingerbroek 2012). In addition, lipids are needed to prevent EFA deficiency.

PN has risks. The central access needed to deliver PN is sometimes associated with nosocomial infection (Stoll 2002). In infants and children who receive PN for more than 14 days, the incidence of parenteral nutrition-associated cholestasis (PNAC) and intestinal failure-associated liver disease is high. Parenteral nutrition-associated liver disease (PNALD) in infants can range from 40% to 85% with long-term use of TPN (Park 2015).

Farnesoid X receptor (FXR) is a nuclear receptor expressed at high levels in the liver and intestine. FXR activity is a major regulator of excretion and metabolism of conjugated bilirubin (Cbil) and bile acid. Studies have demonstrated that plant-derived phytosterols, mainly present in lipid components of PN, act as a potent inhibitor of FXR (Al-Shahwani 2017).

Description of the intervention

LEs serve as a source of high-density energy and a source of EFA, that is linoleic acid (omega-6 fatty acid) and alpha-linolenic acid (omega-3 fatty acid). These are precursors for eicosanoids, which are active in numerous physiological mechanisms, such as platelet function, immune response, inflammation, and early visual and neural development (Driscoll 2008; Koletzko 2001; Lapillonne 2013; SanGiovanni 2000).

Pure soybean oil-based lipid emulsions (S-LEs; e.g. Intralipid, Ivelip, Liposyn III) have been the standard LEs used in neonatal intensive care units (NICUs) worldwide for the last few decades (de Meijer 2009). However, there is evidence to suggest that S-LEs may have harmful effects due to excessive polyunsaturated fatty acid (PUFA) and linoleic acid content (Sala-Vila 2007). Newer LEs aim to decrease the excessive omega-6 fatty acid content by using lipids from sources other than soybean oil.

Medium-chain triglyceride (MCT)-based LEs (coconut oil-derived) decrease the omega-6 content by adding MCT to LEs, for example, Lipovenoes MCT and 20% Lipofundin MCT/long-chain triglyceride (LCT) are a 1:1 mix of MCT and LCT (Vanek 2012). Structured LEs (e.g. Structolipid) are a modification of MCT-LCT-based LEs and are formed by re-esterification of medium- and long-chain fatty acids (Waitzberg 2006). Olive oil-based LEs, which are rich in the monounsaturated fatty acid, oleic acid (18:1; omega-9), have been available since the 1990s. For example, ClinOleic is an olive oil-based LE with a 4:1 ratio of olive to soybean oil and one-third of

the PUFA content compared with S-LE (e.g. 20% Intralipid). Fish oil-containing LEs (e.g. Omegaven), which are rich in omega-3 fatty acids and have a low ratio of omega-6 to omega-3, have also been developed (Wanten 2007).

More recently, LEs derived from multiple sources have become available for clinical use. SMOFLipid is one such LE; it is a 30:30:25:15 mix of soybean oil, MCT, olive oil and fish oil (Sala-Vila 2007). Lipidem, also known as Lipoplus in some countries, is a mix of 50% MCT, 40% soybean oil and 10% fish oil. The lipids and other constituents of various LEs are outlined in Appendix 1.

There is concern that the lipid constituents in breast milk are significantly different compared to the lipid constituents profile (including arachidonic acid, docosahexaenoic acid and eicosapentaenoic acid) in the available LEs (including SMOFLipid) for term and late preterm infants (Scholtens 2009; Appendix 1).

How the intervention might work

Currently available LE formulations differ in the source of lipid, fatty acid profile, antioxidant levels and presence of additional components (Wanten 2007).

Conventional S-LEs contribute to PNALD in term and preterm infants (de Meijer 2009; Xu 2012); phytosterols, present in soybean oil, may have harmful effects on liver function (de Meijer 2009). However, one randomised study found no association of phytosterols with liver dysfunction (Savini 2013). Histologically cholestatic changes in the liver can be detected as early as two weeks after commencement of PN, and evidence of fibrotic changes can be observed within six weeks (Nandivada 2013; Park 2015). The incidence of PNALD increases as the duration of the PN increases; other contributing risk factors include absence of enteral feeding, low birth weight and preterm birth (Park 2015).

High amounts of linoleic acid and alpha-linolenic acid in S-LEs may lead to substrate inhibition of Δ^6 desaturase (Gobel 2003), resulting in decreased formation of arachidonic acid and docosahexaenoic acid, which are crucial for visual and cognitive development in preterm infants (Heird 2005; Lehner 2006). S-LEs also lead to an increase in proinflammatory prostaglandins and leukotrienes (Wanten 2007), which may increase the risk of sepsis (Palmlblad 1991), and may adversely affect phagocytic and lymphocytic functions (Gogos 1995).

S-LEs have excessive amounts of PUFA (up to 60%) and linoleic acid (50%) (Sala-Vila 2007), which exceeds the daily preterm linoleic acid requirement of 0.25 g/kg/day and adds to oxidative stress (Koletzko 2005; Pitkanen 1991).

MCT (coconut oil-derived) and LCT (soybean oil-derived)-based lipid emulsions (MS-LEs) may have advantages due to reduced omega-6 content and the rapid metabolism of MCTs. Data suggest good tolerance in preterm infants with increased eicosapentaenoic acid levels and an equivalent EFA profile compared with S-LEs (Lehner 2006). However, in vitro studies have raised concerns that MCTs may cause leukocyte activation, impair immune function and decrease killing of *Candida albicans* (Waitzberg 2006; Wanten 2007). Use of MCT oil-LEs has also been associated with impaired lung function and aggravation of tissue inflammation in adults with acute respiratory distress syndrome (Lekka 2004); they may

also be ketogenic, which limits their utility in people with acidosis (Waitzberg 2006).

Structured LEs have an even distribution of medium-chain fatty acids in the lipid droplets, aimed at reducing the immunological adverse effects of MS-LEs. There is limited evidence to suggest that structured emulsions are well tolerated in critically ill people; however, unlike MS-LEs, they may not affect phagocyte function (Wanten 2007).

Borage oil-soybean oil-based lipid emulsions (BS-LEs) substitute the soy content partially with borage oil, which is the highest source of gamma-linolenic acid (18:3; omega-6). The enzyme, Δ^6 desaturase, is essential in the conversion from linoleic acid to gamma-linolenic acid and is considered the rate-limiting step in the metabolism from linoleic acid to arachidonic acid. Borage oil-based LEs were developed to potentially circumvent this enzymatic step. PFE 4501 (Pharmacia, Sweden) is a combination of borage oil (15%) and soybean oil (85%) with increased amounts of carnitine to prevent carnitine deficiency in preterm infants (Magnusson 1997).

Olive oil-soybean oil-based lipid emulsions (OS-LEs) have generated interest due to the immune-neutral nature of oleic acid (Reimund 2004), decreased PUFA content, higher alpha-tocopherol content (Sala-Vila 2007), and reduced peroxidability of low-density lipoproteins, with an overall reduction in oxidative stress (Goulet 1999; Krohn 2006). OS-LE (ClinOleic) has been reported to have a fatty acid composition similar to that of breast milk, and to result in higher alpha-tocopherol levels in preterm infants when compared with S-LE (Intralipid; Gobel 2003). Studies have reported decreased immunological disturbance, with lesser inhibition of T-cell activation, lesser effect on interleukin (IL)-2 production and decreased alteration in neutrophil responses with OS-LE compared with S-LE (Buenestado 2006; Gawecka 2008a; Granato 2000). Olecanthol, a minor component in olive oil, inhibits the cyclo-oxygenase pathway but not the 5-lipoxygenase pathway, displaying 'ibuprofen-like' anti-inflammatory activity (Beauchamp 2005). Use of OS-LE may decrease the incidence of hyperglycaemia when compared with S-LE (Intralipid) (Van Kempen 2006). Randomised controlled trials (RCT) of critically ill neonates have shown OS-LE to be as equally well tolerated as conventional S-LE (Gawecka 2008a).

F-LEs have increased omega-3 PUFAs, resulting in inhibition of the cyclo-oxygenase pathway and preferential use of the lipoxygenase pathway, which in turn decreases proinflammatory prostaglandins (Fürst 2000). Eicosapentaenoic acid (C20:5; omega-3), present in fish oil, activates the peroxisome proliferator-activated receptors, alpha and gamma, which in turn antagonise the nuclear factor- κ B signalling pathway, leading to reduced production of inflammatory mediators (Fürst 2000). Adult studies have indicated that, in sepsis, the use of F-LE decreases the length of hospital stay, readmission rates and rate of mechanical ventilation, and improves survival (Wanten 2007). In observational studies, a pure F-LE (Omegaven) decreased and even reversed PNALD in infants, resulting in decreased mortality and lower levels of triglycerides, Cbl and liver enzymes compared with S-LE (20% Intralipid) (de Meijer 2009; Puder 2009). However, one randomised study in infants 34 weeks' gestation and above, undergoing surgery for major gastrointestinal abnormalities, found no difference in incidence of cholestasis with MOFS-LE (SMOFlipid) compared to MCT/LCT-based LE (Pereira-da-Silva 2017).

Multisource LEs (MCT-fish-soybean oil-based lipid emulsions (MFS-LE) and MCT-olive-fish-soybean oil-based lipid emulsions (MOFS-LE) derive the advantages of lipids from multiple sources, including MCTs (rapidly metabolised lipids), soybean oil (EFA source), olive oil (fewer immune effects, and fish oil (anti-inflammatory effects). In one study IL-6 and IL-8 levels were statistically significantly lower with SMOFlipid (MOFS-LE) compared with S-LE in a multivariate analysis adjusting for bronchopulmonary dysplasia and infection (Skouriakou 2016).

There is evidence of reduced hospital stay, better plasma elimination of triglycerides, better alpha-tocopherol levels and good tolerance profile with a MOFS-LE (SMOFlipid) in adults (Grimm 2005; Wanten 2007). An observational study has shown ClinOleic and Omegaven, in a 1:1 combination, decrease cholestasis and the incidence of retinopathy of prematurity requiring laser therapy in preterm infants (Pawlik 2011). Meta-analyses have shown significant decreases in incidence of cholestasis with F-LEs in preterm infants (Kotiya 2016; Vayalthrikkovil 2017).

There is emerging evidence from studies performed in mice that pure F-LEs may have the least impact on hepatic steatosis (Nandivada 2017).

The abbreviation scheme used for the LEs is described in Appendix 2.

Why it is important to do this review

The introduction of life-saving PN was a landmark in neonatal care, but it appears that the conventionally used S-LEs are far from ideal. Despite their widespread use, conventional S-LEs may have harmful effects in infants due to their high PUFA content and phytosterols, which may contribute to adverse outcomes, including mortality, PNALD and sepsis. There is emerging evidence to suggest benefits of fish oil and multisource LE in prevention and resolution of PNALD. The LE of choice in infants would be one that is easy to metabolise, does not increase inflammatory or oxidative stress, is not immunosuppressive, has the least adverse effects and has a proven safety profile. Therefore, we undertook this Cochrane Review to compare all LEs including fish oil-containing LE for prevention or resolution of PNALD, growth and other clinical outcomes in term and late preterm infants with or without surgical conditions or PNALD.

Other systematic reviews on the topic include the systematic review and meta-analysis published by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN), which looks at the role of different LEs in the pathogenesis of cholestasis and PNALD, in a paediatric population including infants (ESPGHAN 2016). Another systematic review and meta-analysis of randomised and observational studies has examined the role of fish oil-containing LE in preventing or reversing PNALD in newborns (Park 2015).

OBJECTIVES

To compare the safety and efficacy of all LE for parenteral nutrition (PN) in term and late preterm infants (between 34 weeks' gestation and 36 weeks' and six days' gestation) with or without surgical conditions or PNALD within first six months of life, using all possible direct comparisons.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

We considered three populations in the current review including:

- term infants (gestational age 37 weeks' or more) and late preterm infants (gestational age between 34 weeks' and 0 days, and 36 weeks' and 6 days) who received intravenous LEs as a part of TPN or PPN at any time in the first six months after birth (for any duration);
- term and late preterm infants with surgical conditions including: necrotising enterocolitis (NEC), gastroschisis, omphalocele, tracheo-oesophageal fistula, intestinal atresia, malrotation, short bowel syndrome, meconium ileus and other surgical conditions;
- term infants and late preterm infants with PNALD/cholestasis (Cbil more than 2 mg/dL (34.2 µmol/L)), with or without raised liver enzymes within the first six months of life.

We excluded infants with cholestasis due to inborn errors of metabolism, biliary atresia or congenital infection.

There were no restrictions on comorbidities including surgery in infants with PNALD.

Types of interventions

We considered studies comparing various LEs, including newer LEs (lipids derived from olive oil, fish oil and MCT; structured lipids, multi-source LEs) and conventional pure S-LEs, in term or late preterm infants.

Eligible lipid emulsions

Soybean oil-based lipid emulsions (S-LEs): LEs with 100% lipids derived solely from soybean oil.

- Intralipid.
- Ivelip.
- Liposyn III.

Fish oil-containing lipid emulsions: all fish oil-containing LEs.

- MCT-olive-fish-soybean oil-based lipid emulsions (MOFS-LEs; e.g. SMOFlipid).
- MCT-fish-soybean oil-based lipid emulsions (MFS-LEs; e.g. Lipidem).
- Pure fish oil (pure F-LE; e.g. Omegaven).

We considered any LE or multicomponent LE that included fish oil as one of the constituents.

Alternative lipid emulsions: all LEs with partial or complete substitution of soybean oil from other sources (decreased linoleic acid content), but not containing fish oil.

- Olive oil-soybean oil-based lipid emulsions (OS-LEs; e.g. ClinOleic).

- MCT-soybean oil-based lipid emulsions (MS-LEs; e.g. Lipovenoes MCT).
- Borage oil-soybean oil-based lipid emulsions (BS-LEs; e.g. PFE 4501).
- Structured lipids (structured MCT-soybean oil; e.g. Structolipid).

See [Appendix 2](#) for a list of abbreviations for eligible LEs and [Appendix 1](#) for lipid constituents.

We considered the following comparisons.

- Fish oil LE versus all non-fish oil LE.
- Fish oil LE versus another fish oil LE.
- Alternative LE versus S-LE.
- Alternative LE versus another alternative LE.

Details of all possible comparisons are noted in [Appendix 3](#).

For term infants with underlying clinical conditions that required PN (surgical conditions) or a change in PN solutions (established cholestasis), we included studies using LEs as a part of TPN or PPN at any time. We did not place restrictions on minimum or maximum dose of LEs.

We placed no restrictions on cointerventions of amino acids, minerals, trace elements or vitamins for PN and expressed breast milk or formula feeds via a nasogastric tube for PPN.

Types of outcome measures

Primary outcomes

- Parenteral nutrition-associated liver disease (PNALD) (conjugated bilirubin ≥ 2 mg/dL (34.2 µmol/L)) with or without raised liver enzymes (alanine aminotransferase (ALT) greater than 45 IU/L, alkaline phosphatase (ALP) greater than 420 IU/L) in the absence of other causes ([Christensen 2007](#); [Robinson 2008](#)), in late preterm and term infants without PNALD at study entry.
- PNALD/cholestasis (any definition).*
- Resolution of PNALD (conjugated bilirubin less than 2 mg/dL (34.2 µmol/L)), in late preterm and term infants with established PNALD ([Lam 2014](#)).
- Physical growth:
 - * days to regain birth weight;
 - * growth rate (g/kg/day) during study period and hospital stay ([Fenton 2017](#)).

Secondary outcomes

- Head growth:
 - * head circumference below third percentile at discharge;
 - * head growth velocity (cm/week).
- Length:
 - * rate of growth;
 - * length velocity (cm/week).
- Body composition: measured at corrected term gestation by magnetic resonance (MR) spectroscopy and magnetic

resonance imaging (MRI) ([Ahmad 2010](#); [Roggero 2007](#); [Uthaya 2016](#)):

- * intrahepatocellular lipid content (IHCL; intrahepatic lipid:water ratio);
- * non-adipose tissue mass.
- Proven sepsis:
 - * blood culture positive;
 - * any sepsis (with or without definition).*
- Necrotising enterocolitis (NEC) stage 2 or greater on Bell's staging system ([Bell 1978](#)).
- Significant jaundice: requiring treatment with phototherapy or exchange transfusion.
- Duration of phototherapy (days).
- Duration of ventilation (total days).
- Duration of supplemental oxygen (total days).
- Need for home oxygen therapy.
- Duration of hospital stay (days).
- Thrombocytopenia (platelets less than 50,000/ μ L).
- Hypertriglyceridaemia, defined by serum triglyceride levels greater than 200 mg/dL (2.25 mmol/L; [Putet 2000](#)).
- Mean conjugated bilirubin (Cbil) levels (μ mol/L).
- Mean gamma-glutamyltransferase (GGT) levels (IU/L).
- Mean alanine aminotransferase (ALT) levels (IU/L).
- Mean alkaline phosphatase (ALP) levels (IU/L).
- Mean triglyceride levels (mmol/L).
- Rate of change of ALT (IU/L/week).*
- Rate of change of Cbil (μ mol/L/week).*
- Time to development of PNALD (days).
- Time to resolution of PNALD (days).
- Hyperglycaemia (blood sugar level greater than 8.3 mmol/L (150 mg/dL; [Sinclair 2011](#)) or hypoglycaemia (blood sugar level less than 2.6 mmol/L (46 mg/dL)).
- Essential fatty acid (EFA) deficiency defined by triene/tetraene ratio greater than 0.05 ([Cober 2010](#); [Gura 2005](#)).
- Other markers of EFA deficiency.
- Need for liver transplantation due to PNALD related liver failure.
- Death before discharge or neonatal death (within the first 28 days of life).
- Neurodevelopmental outcome (assessed by a standardised and validated assessment tool or a child developmental specialist) at any age reported (outcome data grouped at 12, 18 and 24 months if available).

The outcomes marked with asterisk (*) were added after the protocol stage.

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 specialized register](#)). We searched for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed).

Electronic searches

We conducted a comprehensive search including: the Cochrane Central Register of Controlled Trials (CENTRAL, 2018, Issue 5) in the

Cochrane Library; MEDLINE via PubMed (1996 to 18 June 2018); Embase (1980 to 18 June 2018); CINAHL (1982 to 18 June 2018) and MIDIRS (1971 to 31 May 2018). Details for MEDLINE are noted in [Appendix 4](#).

We applied no language restrictions. We searched clinical trial registries for ongoing or recently completed trials (ClinicalTrials.gov, the World Health Organization's International Trials Registry and Platform, and the [ISRCTN Registry](#)).

Searching other resources

We reviewed the reference lists of all identified articles for relevant articles not identified in the primary search.

Data collection and analysis

We used the standard methods of Cochrane Neonatal for data collection and analysis. Data extraction forms were specifically designed for this review, tested on two studies, further refined and then used to collect and collate data. For each included study, we recorded details regarding the method of randomisation, allocation concealment, blinding, intervention, stratification, and whether the study was single-centre or multi-centred. We extracted data regarding participants, PN details and reported outcomes.

We recorded the selection process in sufficient detail to complete a PRISMA flow diagram ([Moher 2009](#)), and [Characteristics of included studies](#) and [Characteristics of excluded studies](#) tables.

Selection of studies

Two review authors (VK, MM) independently searched the databases to identify articles eligible for inclusion in the review. We assessed methodology with regard to blinding of randomisation, allocation concealment, intervention and outcome measurements and completeness of follow-up.

Data extraction and management

Two review authors (VK, MM) separately extracted the data for each study on data extraction forms. One review author (VK) entered data into Review Manager 5 ([Review Manager 2014](#)), and the other review author (MM) cross-checked the printout against his own data extraction forms. At each stage, any difference in opinion was resolved by discussion.

Assessment of risk of bias in included studies

Two review authors (VK, MM) independently assessed the risk of bias (low, high or unclear) of all included trials using the Cochrane 'Risk of bias' tool for the following domains ([Higgins 2017](#)):

- 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.

We resolved any disagreements by discussion or with a third review author (RS). See [Appendix 5](#) for a more detailed description of risk of bias for each domain.

Measures of treatment effect

We followed the recommendations of Cochrane Neonatal, and used a fixed-effect model for meta-analysis. We estimated the treatment effects for categorical outcomes using the typical risk ratio (RR) and typical risk difference (RD) with 95% confidence intervals (CIs). We estimated the number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) if the RD was statistically significant. For continuous outcomes, we used the mean difference (MD) with 95% CIs to describe the data.

Unit of analysis issues

We specified the unit of analysis as the participating infant in individually randomised trials and the NICU for cluster-randomised trials. We did not identify any eligible cluster-randomised trials. If cluster-randomised trials had been included in the analyses, we had planned to adjust their sample size using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2017).

Dealing with missing data

We contacted the authors of included studies if clarifications or additional information were required (Diamond 2017). In the case of missing data, we described the number of participants with missing data in the results section and in the *Characteristics of included studies* table (Table 1).

Assessment of heterogeneity

We estimated treatment effects in individual trials and examined heterogeneity between trials by inspecting forest plots and quantifying the impact of heterogeneity by using the I^2 statistic, a measure that describes the proportion of variation in point estimates that is due to variability across studies rather than sampling error (Deeks 2017). We interpreted the results as follows:

- less than 25%: no heterogeneity;
- 25% to 49%: low heterogeneity;
- 50% to 74%: moderate heterogeneity;
- 75% to 100%: high heterogeneity.

We explored the statistical heterogeneity and the possible causes (e.g. differences in study quality, participants, intervention regimens or outcome assessments) by performing post hoc subgroup analyses.

Assessment of reporting biases

We were not able to use funnel plots to assess publication bias because no outcome had more than ten studies in any comparison (Sterne 2017). We identified and evaluated multiple reports of a single study (multiple publication bias) by comparing the reported baseline characteristics (Table 1), and the author details with clarifications requested from authors, if required, to avoid double-counting.

Data synthesis

We performed meta-analyses using Review Manager 5 (Review Manager 2014), Cochrane's software for preparing and maintaining systematic reviews. For estimates of typical RR and typical RD, we used the Mantel-Haenszel method (Higgins 2017). We used

the inverse variance method for measured quantities. We carried out and reported all primary meta-analyses using the fixed-effect model, according to the recommendations of Cochrane Neonatal.

Details of calculations and imputations

We replaced any standard error of the mean by the corresponding standard deviation (SD). If the data were described in medians and interquartile ranges, we substituted medians for means and imputed the corresponding SDs by dividing interquartile ranges by 1.35. If the data were described in medians and ranges, then we used the formulae proposed by Hozo and colleagues to impute the SD (Hozo 2005).

Where we could not perform meta-analyses, we presented qualitative inferences as systematically as possible and explained why we could not perform meta-analyses. We presented the results for important outcomes in the 'Summary of findings' tables.

Quality of evidence

We used the GRADE approach, as outlined in the *GRADE Handbook* to assess the quality of evidence for the following (clinically relevant) outcomes (Schünemann 2013).

- PNALD (Cbil $\geq$ 2 mg/dL (34.2 μ mol/L)) with or without raised liver enzymes in the absence of other causes (Christensen 2007; Robinson 2008).
- Resolution of PNALD/cholestasis (in infants originally enrolled with underlying liver disease or cholestasis).
- Physical growth:
 - * days to regain birth weight;
 - * growth rate (g/kg/day) during study period and hospital stay (Fenton 2017).
- Head growth:
 - * head circumference below 3% at discharge;
 - * head growth velocity (cm/week).
- Proven sepsis: blood culture positive.
- Hypertriglyceridaemia
- Conjugated bilirubin levels
- ALP levels (IU/L)
- Rate of change in Cbil (μ mol/L/week)
- Death before discharge or neonatal death (within the first 28 days of life).
- Neurodevelopmental outcome (neurodevelopmental outcome assessed by a standardised and validated assessment tool or a child developmental specialist) at any age reported (outcome data grouped at 12, 18 and 24 months if available).

Two review authors (VK, MM) independently assessed the quality of the evidence for each of the outcomes above. We considered evidence from RCTs as high-quality, but downgraded our assessments of the evidence by 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 Guideline Development Tool (GRADEpro GDT 2015) to create 'Summary of findings' tables to report the quality of the evidence.

The GRADE approach results in an assessment of the quality of a body of evidence according to one of the following four grades.

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

We created 'Summary of findings' tables for each comparison; a summary of the risk estimates and the grading of the evidence are provided in the 'Summary of findings' tables.

- **Fish oil LE compared to non-fish oil LE in parenterally fed preterm infants with surgical conditions:** PNALD/cholestasis (conjugated bilirubin ≥ 2 mg/dL; pure F-LE versus S-LE); PNALD/cholestasis (any definition); death before discharge (pure F-LE versus S-LE); neurodevelopmental outcomes (at 6 and 24 months (pure F-LE versus S-LE); culture-positive sepsis (pure F-LE versus S-LE); hypertriglyceridaemia; Cbil levels ($\mu\text{mol/L}$; pure F-LE versus S-LE); ALP levels (IU/L) ([Summary of findings for the main comparison](#)).
- **Fish oil LE compared to non-fish oil LE for parenterally fed preterm infants with cholestasis:** resolution of PNALD/cholestasis (conjugated bilirubin less than 2 mg/dL) (pure fish oil-LE versus S-LE); PNALD/cholestasis (any definition) (all fish oil LE versus non-fish oil LE; growth rate (g/week; pure F-LE versus S-LE); death before discharge (all fish oil-LE versus S-LE); any sepsis (all fish oil-LE versus S-LE); hypertriglyceridaemia; Cbil levels ($\mu\text{mol/L}$; MOFS-LE versus S-LE); ALP levels (IU/L); rate of change of conjugated bilirubin ($\mu\text{mol/L/week}$) ([Summary of findings 2](#)).

Subgroup analysis and investigation of heterogeneity

We explored high statistical heterogeneity in the outcomes by visually inspecting the forest plots and by removing the outlying studies in the sensitivity analysis ([Deeks 2017](#)). Where statistical heterogeneity was significant, we interpreted the results of the meta-analyses accordingly; and we downgraded the quality of the evidence in the 'Summary of findings' tables, according to the GRADE recommendations as applicable.

For some outcomes, if there was significant heterogeneity and there were only two studies in an outcome with limited samples, we did not perform meta-analysis and described the results from the two studies.

We considered the following groups for subgroup analysis where specific subgroup data are available.

- Age of enrolled infants (first week versus later).
- Sex.
- Gestational age: term infants (gestational age 37 weeks or more); late preterm infants (gestational age between 34 weeks and 0 days, and 36 weeks and 6 days).
- Lipid dosing (actual dose received daily; cumulative).
- Continuous intravenous lipid versus intermittent intravenous lipid.

However, the subgroup data on any of the predefined subgroups was not available.

Sensitivity analysis

We decided to present the results of the sensitivity analyses only if these were significantly different from the primary results. We pre-decided to do the sensitivity analysis in the following situations.

- If there was unexplained moderate to high heterogeneity, we explored this by removing the outlying study/studies causing heterogeneity (if feasible).
- If a study with high risk of (material) bias was included in the meta-analysis of an outcome where the other studies had low risk of bias, we removed the study with high risk of bias and evaluated the results.

However, in outcomes where there were only two studies, the sensitivity analysis was not applicable.

RESULTS

Description of studies

We included nine studies ($n = 273$) in the review with six studies ($n = 182$) contributing data to the evidence synthesis and meta-analyses for the outcomes of interest in this review ([Characteristics of included studies](#) table).

Results of the search

The search yielded 1673 articles from medical literature databases and 88 clinical trial registry reports. We removed duplicates for a total of 1164 records. We excluded 1141 records based on titles and abstracts and assessed 23 full-text articles for eligibility. We excluded 14 full-text articles with reasons. Five studies were excluded after discussion between authors (VK, MM) ([Characteristics of excluded studies](#) table). We included nine studies in the review ([Characteristics of included studies](#) table). We reported the study selection process in the PRISMA flow diagram ([Figure 1](#)).

Figure 1. PRISMA flow diagram.

Included studies

Angsten 2002 was a double-blind, randomised trial performed at the Department of Paediatric Surgery, University Children's Hospital, Uppsala, Sweden.

- Population: inclusion criteria were neonates of either sex with a gestational age of 36 to 41 weeks at birth, birthweight of 2.5 g to 4.0 kg, and a postnatal age of up to four days, needing surgical treatment and requiring TPN for a minimum of five days. Neonates needing surgery for various oesophago-gastrointestinal malformations were assigned before surgery. Exclusion criteria were metabolic disease, renal disease, inflammatory disease, septic syndrome or a haematological disorder.
- Objectives: to determine whether MCT-based LEs were more efficient in producing energy than pure LCT-based LEs without adverse effects.
- Interventions: treatment group (n = 10) received Vasolipid, containing 50% MCT and 50% LCT and the control group (n = 10) received Intralipid. The total amount of fat infused on the first day was 2 g/kg/day and this amount was increased at a daily rate of 0.5 g/kg/day until an infusion rate of 3 g/kg/day was reached. Before the start of TPN, after five days of TPN and five hours after the LE ended, two blood

samples (2.5 mL) were taken for measurement of free and total plasma carnitine concentrations, free fatty acids, fatty acid composition of plasma cholesterol esters, phospholipids, triglycerides and ketones as b-hydroxybutyrate. A piece of adipose tissue weighing approximately 15 mg and a piece of muscle weighing approximately 30 mg were taken during surgery as an open biopsy with a scalpel.

- Outcomes: primary outcomes: fatty acid compositions in the plasma and adipose tissue and carnitine concentrations in the plasma and muscle. Secondary outcomes: heart rate, body temperature, bodyweight and clinical symptoms were recorded daily. Haematological (haemoglobin, leukocytes and platelets) and biochemical (aspartate aminotransferase, ALT, sodium, potassium, creatinine, ALP, albumin and bilirubin) parameters were measured on day 0, just before the first infusion of TPN started, and after termination of the study.

Ariyawangso 2014 was a prospective, open-label and randomised study in surgical neonates conducted between 1 March 2013 and 30 November 2013 at Queen Sirikit National Institute of Child Health, Bangkok, Thailand.

- Population: surgical neonates with gastroschisis, omphalocele, jejuno-ileal atresia or duodenal atresia requiring PN for at least seven consecutive days were eligible to

participate in the study. Infants were excluded if they had already received PN. Additional exclusion criteria included neonates with the following conditions: Down's syndrome, severe congenital malformations, patent ductus arteriosus (PDA), anuria due to circulation failure, liver/haemolytic diseases, hepatitis, thrombocytopenia, HIV, oxygen saturation (SO₂) less than 80% for more than two hours, severe acidosis, application of catecholamines, multiorgan failure, hypoxic-ischaemic encephalopathy, shock and sepsis.

- Objectives: to assess the safety and efficacy of 20% SMOFlipid in surgical neonates receiving PN compared with an S-LE (20% Intralipid).
- Interventions: 42 surgical infants requiring PN allocated to receive either SMOFlipid (n = 21) or Intralipid (n = 21). The LE was started parenterally at 0.5 g/kg/day on day 1 and was increased by increments of 0.5 g/kg/day daily up to 3.0 g/kg/day for term and 3.5 g/kg/day for preterm neonates, until it reached 50% of total energy intake. Blood samples were collected for assessment of primary and secondary outcomes on day 0, 8, 15 and 22 of the study if PN was continued.
- Outcomes: primary outcomes: safety outcomes including liver enzymes ALT, aspartate aminotransferase, ALP, GGT, total bilirubin, conjugated bilirubin, lipid profile, blood urea nitrogen, serum creatinine and haematological parameters. Secondary outcomes: efficacy outcomes including infant's weight, head circumference and length at study entry and exit were recorded.

Diamond 2017 was a multicentre parallel-group RCT with 1:1 assignment comparing SMOFlipid with Intralipid for the prevention of progression of Intestinal failure associated liver disease (IFALD) in infants.

- Population: primary inclusion criteria were an infant aged less than 24 months with short bowel syndrome or intestinal failure who received substantial PN support (greater than 40% total calories) and was demonstrating early hepatic dysfunction (Cbil 17 µmol/L to 50 µmol/L (1 mg/dL to 3 mg/dL)) in the absence of sepsis. The study was included in the current review as the age of all the participants at study entry was less than 9 weeks. Exclusion criteria: sepsis or haemodynamic instability; coagulopathy (platelets ≤ 150 000/µL, or international normalised ratio (INR) ≥ 1.4); hypersensitivity to fish, egg or soy protein or to any of the active substances or excipients; current enrolment in another clinical trial involving a surgical or pharmacological intervention; serum Cbil greater than 50 µmol/L; hyperlipidaemia; treatment with intravenous N-acetylcysteine or oral ursodeoxycholic acid; renal insufficiency; fluid imbalance and unstable medical conditions.
- Objectives: to examine whether SMOFlipid prevented progression of IFALD in PN-dependent infants with early IFALD (Cbil 17 µmol/L to 50 µmol/L (1 mg/dL to 3 mg/dL)).
- Interventions: participants received trial lipid for up to 12 weeks. Participants also ended the trial if they achieved full enteral tolerance prior to this time or if they developed progressive liver disease defined by a serum Cbil exceeding 100 µmol/L for greater than 14 days. The PN solution was formulated according to a nomogram that took into account the proportion of caloric intake received parenterally. Choice of feeds, timing of the adjustment of the enteral feeds and ratio of enteral to parenteral feeds were at the discretion of the treating physician.

- Outcomes: the primary end point for analysis was Cbil the week that the child received his or her last dose of trial lipid (at 12 weeks, at full enteral tolerance or on the development of progressive liver disease). Other data collected at baseline, weekly while on the trial and 4 weeks following trial completion (referred to as "post-trial") included serum Cbil, serum albumin, liver enzymes, parenteral intake and enteral intake.

Magnusson 1997 was a double-blind, RCT performed at the Department of Pediatric Surgery, University Hospital Uppsala, Sweden.

- Population: neonates undergoing surgery for various oesophago-gastrointestinal malformations were assigned the day after surgery to either Intralipid (control group) or PFE 4501 (treatment group) in a double-blind, randomised manner.
- Objectives: to compare Intralipid with PFE 4501 in neonates with special reference to changes in fatty acid composition in plasma and adipose tissue, plasma carnitine concentrations and tolerance during a short period of TPN.
- Interventions: 20 neonates received Intralipid (n = 10) or PFE (n = 10). Inclusion criteria were neonates of either sex needing surgical treatment, age up to and including seven days, and requiring TPN for a minimum of five days. The exclusion criteria were metabolic disease, renal disease, inflammatory disease, septic syndrome or a haematological disorder. The total amount of fat infused was 2 g/kg on the first day and increased at a daily rate of 1 g/kg until a rate of 4 g/kg/day was reached.
- Outcomes: primary outcomes: to examine the changes in fatty acid composition in plasma and adipose tissue, plasma carnitine concentrations and tolerance during a short period of TPN. Heart rate, body temperature, bodyweight and clinical symptoms were recorded daily. Haematological (haemoglobin, leukocytes and platelets) and biochemical (aspartate aminotransferase, ALT, sodium, potassium, creatinine, ALP, albumin and bilirubin) parameters were measured on day zero, just before the first infusion of TPN started, and after termination of the study.

Lam 2014 was a prospective, double-blind, RCT conducted at a level III university-affiliated NICU, one of three tertiary referral centres for neonatal surgery in Hong Kong.

- Population: inclusion criteria included Cbil 34 µmol/L or greater (2 mg/dL), likely to require PN for more than 2 weeks and informed parental consent. The exclusion criteria were major congenital or lethal chromosomal abnormalities, multiorgan failure or imminent death, and cholestatic jaundice secondary to other known causes, for example congenital or acquired TORCH (acronym for a group of diseases that cause congenital conditions; **T**oxoplasmosis, **O**ther (such as syphilis, varicella, mumps, parvovirus and HIV), **R**ubella, **C**ytomegalovirus, **H**erpes simplex), syphilis, hepatitis B or C infection, biliary atresia, or other intra- or extrahepatic diseases obstructing bile flow.
- Objectives: to evaluate whether pure F-LE could halt or reverse the progression of PNAC compared with soy-based parenteral lipid preparation (SLP) and to assess the effects of pure F-LE on liver function and physical growth.
- Intervention: infants were randomly assigned to receive either pure F-LE (10% Omegaven; Fresenius-Kabi AG, Bad Homburg vor der Höhe, Germany) or S-LE (10% Intralipid; Fresenius-Kabi AG, Uppsala, Sweden). Pharmacists not involved in the care of the

infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period. Infants randomised to the pure F-LE arm received a starting dose of 0.5 g/kg/day and gradually advanced to the maximum of 1.5 g/kg/day at 0.5 g/kg/day increments every two days.

- Outcomes: the primary outcome was reversal of PNAC, defined as Cbil less than 34 $\mu\text{mol/L}$ within four months after commencement of lipid treatment. The secondary outcomes were rate of change of weekly liver function tests, infant growth parameters (namely head circumference and bodyweight), blood lipid profile and number of episodes of late-onset infection.

Larsen 2012 was a double-blind, randomised, controlled clinical trial performed at The Stollery Children's Hospital Edmonton, AB, Canada. Study enrolment: November 2005 to March 2007. Larsen 2015 (an additional reporting of **Larsen 2012**) reported on lymphocytes, fatty acids and procalcitonin levels. Relevant data were extracted from both study reports.

- Population: Infants scheduled to have open heart surgery who were appropriate-for-gestational-age and had Apgar scores greater than 7 at five and 10 minutes, and no clinical or microbiological evidence of infection preoperatively, were included in the study. Infants were randomised to receive one of two intravenous lipid preparations: the control group received an emulsion composed exclusively of S-LE (Intralipid; Clintec Nutrition Company, Baxter, Deerfield, IL, USA), while the treatment group received an emulsion containing 50% MCTs and 40% LCTs from soybean oil and 10% fish oil (MLF 541, Lipoplus; B Braun Melsungen, Melsungen, Germany). Exclusion criteria: infants receiving immunosuppressive or anti-inflammatory drugs (e.g. indomethacin, aspirin).
- Objectives: investigated the effects of providing an LE supplemented with ω -3 lipids and MCT on plasma lymphocytes and procalcitonin concentrations in critically ill infants following open heart surgery with cardiopulmonary bypass (CPB).
- Interventions: 32 infants undergoing CPB and dependent on PN were randomised to receive either S-LE (control, $n = 16$) or a 50:40:10 mixture of MCT, soybean oil and fish oil (treatment, $n = 16$). PN was administered for three days preoperatively and 10 days postoperatively.
- Outcomes: Fatty acids (eicosapentanoic acid, arachidonic acid, linolenic acid, linoleic acid, docosahexanoic acid), lymphocytes, granulocyte macrophage-colony stimulating factor (GM-CSF) and inflammatory markers were quantified at baseline; before surgery; and days 1, 7 and 10 after surgery. The measured inflammatory markers included: leukotriene B₄, tumour necrosis factor- α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-8 and IL-10 interferon-gamma. The study also reported on the clinical outcomes including length of stay, duration of ventilation and sepsis incidence.

Lima 1988 was a single-centre RCT performed at the Departments of Child Health and Medical Biochemistry, University of Wales College of Medicine, Cardiff, UK.

- Population: inclusion criteria were nil by mouth, total serum bilirubin less than 100 $\mu\text{mol/L}$ and tolerating intravenous nutrition. Infants had a variety of illnesses such as respiratory problems requiring ventilation and major neonatal abdominal

surgery. The population included infants with gestations as low as 25 weeks.

- Objectives: to investigate how parenteral MCT was tolerated by newborns requiring PN. The clinical and biochemical effects of a 50% MCT/50% LCT-based LE were compared with conventional 100% LCT (S-LE) emulsion in terms of weight gain, plasma triglycerides, cholesterol, ketones, free fatty acids and glucose.
- Interventions: 51 infants were enrolled: group 1 ($n = 26$) received 50% MCT/50% LCT-based LE and group 2 ($n = 25$) received the conventional 100% LCT emulsion. All neonates received similar parenteral infusates, apart from the LE. Amino acid solution-Vamin 9 (KabiVitrum) was started on the third day of life in an increasing dosage schedule up to 2.1 g/kg/day of amino acids. LE was administered on day four, either as Lipofundin MCT/LCT (B Braun Medical) or as Intralipid (KabiVitrum), at initial doses of 0.5 g/kg/day for infants of less than 1.5 kg birthweight and 1 g/kg/day for infants 1.5 kg birthweight or more. LE was increased daily by 0.5 g/kg up to a maximum of 3 g/kg/day. The LEs were infused by the same route using a 'Y' connection tube near the infant for 20 hours per day. Blood samples (1 mL) were collected at 9 a.m. before the daily lipid infusion was started. Samples were taken daily up to the seventh day of lipid administration and then weekly until the infants were discharged from the study.
- Outcomes: clinical and biochemical effects including weight gain, plasma triglycerides, cholesterol, ketones, FFA and glucose.

Nehra 2014 was a randomised, controlled, double-blind clinical trial at Boston Children's Hospital, Boston, MA, USA. This trial is registered at ClinicalTrials.gov (NCT 00512629). Study enrolment was July 2007 to June 2009.

- Population: inclusion criteria: neonates and infants (less than three months of age) with baseline conjugated bilirubin less than 1.0 mg/dL and a gastrointestinal disease requiring surgical intervention who were expected to be PN dependent for 21 days or more. Exclusion criteria: baseline INR greater than 1.5 (greater than 2 if one week of age or less) or triglyceride level greater than 400 mg/dL and infants with a haemolytic disorder, liver disease or shock requiring vasopressor support, extracorporeal membrane oxygenation, nitric oxide, or a combination of these; infants who had undergone an intestinal lengthening procedure.
- Objectives: to assess the safety and efficacy of an intravenous pure F-LE in reducing the incidence of cholestasis in neonates compared with the traditional S-LE in infants requiring surgery for gastrointestinal disorders.
- Interventions: S-LE (Intralipid; $n = 10$) versus pure F-LE (Omegaven; $n = 9$). Infants received standard medical, surgical and nutrition support. Both LEs were provided at 1 g/kg/day, and this dose was kept constant throughout the study period. All infants remained on their assigned LE until weaned from PN unless crossed over to the other study arm. Infants with persistently elevated conjugated bilirubin (greater than 2 mg/dL for two or more continuous weeks) were considered treatment failures and were crossed over to the other study arm.
- Outcomes: to determine whether the incidence of cholestasis, defined as a serum conjugated bilirubin greater than 2 mg/dL for two or more consecutive weeks, differed between the S-LE and pure F-LE. Secondary outcomes evaluated the safety and tolerability of the pure F-LE compared with the S-

LE. Safety evaluation of the pure F-LE involved assessment of mortality and adverse event rate including infections, cardiopulmonary arrest and incorrect LE dosing. Additional safety evaluation included an analysis and comparison of growth parameters, bleeding complications, transfusion requirements, laboratory studies and neurodevelopmental outcomes. Neurodevelopmental outcome was assessed by Bayley Scales of Infant and Toddler Development, 3rd edition (BSID-III), a series of motor, cognitive, and language scales, at 6 and 24 months' corrected age.

[Pereira-da-Silva 2017](#) was a single-centre, double-blind, RCT that compared the incidence of cholestasis using either SMOFlipid or MCT/SOY in neonates born at 34 weeks or greater gestational age undergoing major surgery. The study was performed at the NICU, Hospital Dona Estefania, Lisbon, Portugal. Recruitment was from August 2011 to February 2014.

- Population: inclusion criteria were infants at 34 or more gestational weeks who underwent surgery for a major anomaly of the digestive tract or of a congenital anomaly affecting the digestive tract (e.g. diaphragmatic hernia). Neonates were recruited within the first 48 postnatal hours, if PN had been initiated. Exclusion criteria were pre-existing hepato-biliary disease and abnormal liver functions within the first 72 postnatal hours.
- Objectives: to examine the effects of two LE: either 30% soybean oil, 30% MCT, 25% olive oil and 15% fish oil (SMOFlipid) or 50% MCT and 50% soybean oil n-6 (MCT/SOY; MS-LE) on the incidence of cholestasis in surgical term and near-term neonates.
- Intervention: 49 infants received SMOFlipid (n = 22) or MCT/SOY (n = 27). All participants were scheduled to receive an individualised PN within the first 24 postnatal hours, including amino acids, glucose, electrolyte and vitamin PN solution plus lipids (using SMOFlipid or MCT/SOY). As customised PN was not available during the weekends, infants admitted over weekends

received a standard solution containing only glucose, calcium and amino acids. Parenteral lipid intake was reduced to 0.5 g/kg/day to 1.5 g/kg/day if there was hypertriglyceridaemia (greater than 250 mg/dL), hyperglycaemia (greater than 150 mg/dL), unconjugated bilirubin greater than 12 mg/dL, acute phase of sepsis or pulmonary hypertension. If cholestasis was diagnosed, the parenteral intakes were limited to no more than 2 g/kg/day to 2.5 g/kg/day of lipids, 2 g/kg/day to 2.5 g/kg/day of amino acids and 12 mg/kg/minute of glucose. The same enteral feeding protocol was used in both groups. Minimal enteral feeding (10 mL/kg daily for five days) was initiated.

- Outcomes: primary outcome was incidence of cholestasis, defined initially as Cbil greater than 1 mg/dL (17.1 mmol/L). After the trial initiation, the primary outcome was modified (i.e. Cbil greater than 1 mg/dL (17.1 mmol/L) if total bilirubin was less than 5 mg/dL (85.5 mmol/L) or a Cbil greater than 20% of the total bilirubin if this was greater than 5 mg/dL). Secondary outcome was initially set as the severity of cholestasis, evaluated by the magnitude of the conjugated hyperbilirubinaemia and GGT greater than 225 IU/L. After the trial initiation, the definition was modified to include total ALP greater than 608 IU/L; elevated serum ALT and aspartate aminotransferase (AST), defined as greater than 55 IU/L in girls or greater than 60 IU/L in boys, as markers of PNALD.

Excluded studies

We excluded five studies after discussion among the authors (VK, MM) ([Calkins 2014](#); [Calkins 2017](#); [Nehra 2013](#); [Pichler 2014](#); [Webb 2008](#)). The full details of these excluded studies are provided in the [Characteristics of excluded studies](#) table. The full PRISMA flow chart of the review is provided in [Figure 1](#).

Risk of bias in included studies

We used the Cochrane 'Risk of bias' tool to evaluate the studies. The risk of bias summary is provided in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random 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)	Other bias
Angsten 2002	?	?	?	+	+	?	+
Ariyawangso 2014	?	-	?	?	-	?	+
Diamond 2017	+	+	+	+	+	+	+
Lam 2014	+	+	+	+	+	+	?
Larsen 2012	+	+	+	+	+	+	?
Lima 1988	+	?	?	?	+	?	+
Magnusson 1997	?	?	?	+	+	?	+
Nehra 2014	+	+	+	+	?	+	?
Pereira-da-Silva 2017	+	+	+	+	+	?	?

Allocation

All included studies were described as randomised. However, six studies adequately described the method of the random sequence generation and were at low risk of bias (Diamond 2017; Lam 2014; Larsen 2012; Lima 1988; Nehra 2014; Pereira-da-Silva 2017). Three studies did not describe the randomisation procedure and were at unclear risk of bias (Angsten 2002; Ariyawangso 2014; Magnusson 1997).

Five studies described allocation concealment using the pharmacy/central allocation and were at low risk of bias (Diamond 2017; Lam 2014; Larsen 2012; Nehra 2014; Pereira-da-Silva 2017). In three studies, there was insufficient information regarding concealment of allocation (Angsten 2002; Lima 1988; Magnusson 1997). One study was at high risk for allocation concealment (Ariyawangso 2014). This was an open-label study with blocked randomised design and authors did not describe measures to conceal allocation. Blocked randomised designs can be at particular risk that the blocks can be guessed.

Blinding

Five studies adequately described the blinding of the intervention and control LE as being identical (low risk; Diamond 2017; Lam 2014; Larsen 2012; Nehra 2014; Pereira-da-Silva 2017). Three studies were described as blinded but did not report how blinding was achieved (unclear risk; Angsten 2002; Lima 1988; Magnusson 1997). Two studies were assigned low risk for detection bias by author consensus as the reported outcomes were objective (Angsten 2002; Magnusson 1997). One study was described as an open-label study and was assigned unclear risk of bias by author consensus as the reported outcomes were objective (Ariyawangso 2014).

Incomplete outcome data

Seven studies were at low risk of attrition bias or incomplete outcome data (Angsten 2002; Diamond 2017; Lam 2014; Larsen 2012; Lima 1988; Magnusson 1997; Pereira-da-Silva 2017). One study reported clinical outcomes for most infants but secondary outcome of neurodevelopment outcome had loss to follow-up; however, the data for neurodevelopment were not used in the meta-analysis (unclear risk; Nehra 2014). One study did not include data of all infants for the outcomes of liver enzymes (high risk; Ariyawangso 2014). Ariyawangso 2014 reported data on 24/41 (57%) enrolled infants. The study report mentioned that 18 neonates (n = 8 in the control group and n = 10 in the experimental group) had recovered by day 22 (the day of outcome investigation) and only 24 surgical infants remained in the study.

Selective reporting

Four studies provided trial registration information with published study details (Diamond 2017; Lam 2014; Larsen 2012; Nehra 2014) and were assigned low risk of bias for selective reporting. Trial registration information for one of the studies was dated after the trial completion and pre-specified protocol or study details were not available to us. Therefore this study (Pereira-da-Silva 2017) was assigned unclear risk of bias for selective reporting. Reporting bias was unclear for the other four studies where protocols were not available. Some studies mainly reported biochemical outcomes (Angsten 2002; Larsen 2012; Magnusson 1997).

Other potential sources of bias

Three out of five studies that contributed data to the various outcomes of the review were terminated early and the risk of bias was not clear though it did further decrease the number of infants in the outcomes. The reasons for the study terminations included: non-availability of LE preparation (Pereira-da-Silva 2017), parents refusing participation or agreeing for randomisation (Lam 2014), and low prevalence of cholestasis in the cohort (Nehra 2014).

Effects of interventions

See: **Summary of findings for the main comparison** Fish oil LE compared to non-fish oil LE in infants with surgical conditions for parenterally fed term and late preterm infants; **Summary of findings 2** Fish oil LE compared to non-fish oil LE in infants with cholestasis for parenterally fed term and late preterm infants

The search identified nine studies (n = 273) for inclusion in the review.

As per the review protocol (Kapoor 2018), we considered all possible LE comparisons in term and late preterm populations (i.e. including infants without any PNALD/surgery, infants with surgical conditions and infants with pre-existing cholestasis).

There was wide variation in gestation and weight at birth in the studies of infants with surgical conditions or cholestasis, often with mixed gestations including term and preterm infants.

Table 1 provides baseline characteristics of participants.

Term and late preterm infants without PNALD or surgical conditions

No studies compared LE in term and late preterm infants without underlying cholestasis or surgical conditions.

Term and late preterm infants with surgical conditions

There were seven studies performed in infants with surgical conditions. Of these, four studies compared fish oil LE versus non-fish oil LE (Ariyawangso 2014; Larsen 2012; Nehra 2014; Pereira-da-Silva 2017), and three studies compared alternative-LE versus S-LE (Angsten 2002; Lima 1988; Magnusson 1997).

Fish oil LE versus non-fish oil LE in infants with surgical conditions (Comparison 1)

Three studies (n = 110) compared fish oil LE versus non-fish oil LE in infants with surgical conditions that provided data which could be used in evidence synthesis and meta-analysis (Ariyawangso 2014; Nehra 2014; Pereira-da-Silva 2017).

PNALD/cholestasis (conjugated bilirubin 2 mg/dL or greater) (outcome 1.1)

PNALD/cholestasis was defined as Cbil 2 mg/dL or greater in the review protocol (Kapoor 2018). One study that provided data for cholestasis in surgical infants defined PNALD/cholestasis using the cut-off of greater than 2 mg/dL for two or more consecutive weeks (Analysis 1.1; Nehra 2014). One infant in each arm had cholestasis (treatment failure in the study) over a period of two years. Therefore the interim analysis was performed with an intention of potentially revising the study design. However, the study was terminated prematurely. The LEs were provided at 1 g/kg/day in both arms.

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.11, 95% CI 0.08 to 15.28; typical RD 0.01, 95% CI -0.27 to 0.29; $n = 19$; very low-quality evidence).

PNALD/cholestasis (any definition) (outcome 1.2)

We also considered an outcome for PNALD using any definition of cholestasis.

Two studies reported data that could be used for the meta-analysis (Analysis 1.2; Nehra 2014; Pereira-da-Silva 2017). One study defined cholestasis as Cbil greater than 1 mg/dL if total bilirubin was less than 5 mg/dL and greater than 20% if total bilirubin was greater than 5 mg/dL (Pereira-da-Silva 2017). The other study used the cut-off of greater than 2 mg/dL for two or more consecutive weeks to define cholestasis (Nehra 2014).

In the subgroup comparison between MOFS-LE and MS-LE, one study reported data with no statistically significant difference between groups (typical RR 1.23, 95% CI 0.35 to 4.35; typical RD 0.03, 95% CI -0.18 to 0.24; $n = 49$; Pereira-da-Silva 2017).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.11, 95% CI 0.08 to 15.28; typical RD 0.01, 95% CI -0.27 to 0.29; $n = 19$; Nehra 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR 1.20, 95% CI 0.38 to 3.76; typical RD 0.03, 95% CI -0.14 to 0.20; 2 studies; $n = 68$; low-quality evidence). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$).

Culture-positive sepsis (outcome 1.3)

Two studies reported data on culture positive sepsis (Analysis 1.3; Larsen 2012; Nehra 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.11, 95% CI 0.39 to 3.19; typical RD 0.04, 95% CI -0.40 to 0.49; $n = 19$; Nehra 2014).

In the subgroup comparison between MFS-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.00, 95% CI 0.30 to 3.32; typical RD 0.00, 95% CI -0.30 to 0.30; $n = 32$; Larsen 2012).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR 1.05, 95% CI 0.47 to 2.34; typical RD 0.02, 95% CI -0.23 to 0.27; 2 studies; $n = 51$; very low-quality evidence). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$).

Any sepsis (clinical or culture positive (or both)) (outcome 1.4)

Three studies provided data that could be used in this meta-analysis (Analysis 1.4; Ariyawangso 2014; Larsen 2012; Nehra 2014). One study reported sepsis in the whole study population but data were not available separately for LE groups (Pereira-da-Silva 2017).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.11, 95% CI 0.39 to 3.19; typical RD 0.04, 95% CI -0.40 to 0.49; $n = 19$; Nehra 2014).

In the subgroup comparison between MFS-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.00, 95% CI 0.41 to 2.45; typical RD 0.00, 95% CI -0.34 to 0.34; $n = 32$; Larsen 2012).

One study comparing MOFS-LE versus S-LE reported data on sepsis with no statistically significant difference between groups (typical RR 1.00, 95% CI 0.07 to 14.95; typical RD 0.00, 95% CI -0.13 to 0.13; $n = 42$; Ariyawangso 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR 1.04, 95% CI 0.53 to 2.02; typical RD 0.01, 95% CI -0.15 to 0.17; 3 studies; $n = 93$). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$).

Necrotising enterocolitis (any stage) (outcome 1.5)

One study comparing MOFS-LE versus S-LE reported data on NEC using Bell's stage 1 or 2 (Ariyawangso 2014). No study reported on NEC stage 2 or greater. This study reported three episodes of NEC in both groups and appeared to have provided this result for the whole cohort of participants.

There was no statistically significant difference between groups (typical RR 1.00, 95% CI 0.23 to 4.40; typical RD 0.00, 95% CI -0.21 to 0.21; $n = 42$; Analysis 1.5).

Duration of ventilation (outcome 1.6)

One study reported data on ventilation duration with no statistically significant difference between groups (MD 2.10 days, 95% CI -0.95 to 5.15; $n = 32$; Analysis 1.6; Larsen 2012).

Length of stay (outcome 1.7)

One study reported data on length of stay with no statistically significant difference between groups (MD 5.10 days, 95% CI -9.59 to 19.79; $n = 32$; Analysis 1.7; Larsen 2012).

Hypertriglyceridaemia (outcome 1.8)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.8; Nehra 2014; Pereira-da-Silva 2017). The study reports used the cut-off for reporting as 250 mg/dL (Pereira-da-Silva 2017) and 300 mg/dL (Nehra 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported no infants with hypertriglyceridaemia (typical RR not estimable; typical RD 0.00, 95% CI -0.18 to 0.18; $n = 19$; Nehra 2014).

In the subgroup comparison between MOFS-LE and MS-LE, one study reported data with statistically significant effect in favour of MOFS-LE (typical RR 0.25, 95% CI 0.06 to 1.01; typical RD -0.28, 95% CI -0.50 to -0.06; $n = 49$; Pereira-da-Silva 2017).

There was moderate to high heterogeneity for RD ($I^2 = 81\%$ for between-study heterogeneity and 73% for subgroup differences). There were only two studies in this outcome precluding any sensitivity analysis. Therefore, we did not perform the meta-analysis and have presented the results of both studies separately.

Conjugated bilirubin levels (outcome 1.9)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.9; Ariyawangso 2014; Nehra 2013).

One of the studies in this outcome only provided data for 24/42 (about 57%) participants enrolled in the study (Ariyawangso 2014). Authors mentioned "on day 22 of the study, there were 24 surgical neonates remaining in the study (n = 13 in the control group and n = 11 in the experimental group) as 18 neonates (n = 8 in the control group and n = 10 in the experimental group) had recovered." Ariyawangso 2014 reported almost four times higher mean levels of Cbil in the S-LE group; however, there were no statistically significant differences between the mean ALT, ALP or GGT levels in the two groups. The mean duration of LE was approximately three weeks in both LE groups in this study.

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with statistically significant effect in favour of MOFS-LE (MD -33.52 µmol/L, 95% CI -50.60 to -16.44; n = 24; Ariyawangso 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD 0.00 µmol/L, 95% CI -11.30 to 11.30; n = 14; Nehra 2014).

There was high heterogeneity among the subgroups ($I^2 = 90\%$) with one of the studies which showed a statistically significant difference was also at a high risk of bias (Ariyawangso 2014).

The other study in this outcome showed no statistically significant difference in the conjugated bilirubin levels (Nehra 2014). Therefore, we presented the results of both studies separately rather than performing a meta-analysis.

Gamma-glutamyltransferase levels (outcome 1.10)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.10; Ariyawangso 2014; Nehra 2014).

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (MD 63.68 IU/L, 95% CI -44.12 to 171.48; n = 24; Ariyawangso 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -53.00 IU/L, 95% CI -205.64 to 99.64; n = 14; Nehra 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (MD 24.85 IU/L, 95% CI -63.21 to 112.91; 2 studies; n = 38). There was low heterogeneity among the subgroups ($I^2 = 33.2\%$).

Alanine aminotransferase levels (outcome 1.11)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.11; Ariyawangso 2014; Nehra 2014).

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -2.80 IU/L, 95% CI -15.80 to 10.20; n = 24; Ariyawangso 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -7.00 IU/L, 95% CI -26.75 to 12.75; n = 14; Nehra 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (MD -

4.07 IU/L, 95% CI -14.93 to 6.79; 2 studies; n = 38). There was no heterogeneity among the subgroups ($I^2 = 0\%$).

Alkaline phosphatase levels (outcome 1.12)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.12; Ariyawangso 2014; Nehra 2014).

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -48.96 IU/L, 95% CI -112.35 to 14.43; n = 24; Ariyawangso 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -96.00 IU/L, 95% CI -236.52 to 44.52; n = 14; Nehra 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (MD -56.91 IU/L, 95% CI -114.70 to 0.87; 2 studies; n = 38; low-quality evidence). There was no heterogeneity among the subgroups ($I^2 = 0\%$).

Triglyceride levels (outcome 1.13)

Two studies reported data in a format that could be used for the meta-analysis (Analysis 1.13; Ariyawangso 2014; Nehra 2014).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -0.12 mmol/L, 95% CI -0.61 to 0.37; n = 14; Nehra 2014).

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (MD 0.18 mmol/L, 95% CI -0.56 to 0.92; n = 24; Ariyawangso 2014).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (MD -0.03 mmol/L, 95% CI -0.44 to 0.38; 2 studies; n = 38). There was no heterogeneity among the subgroups ($I^2 = 0\%$).

Rate of change of conjugated bilirubin

One study (Ariyawangso 2014) provided data on change of direct bilirubin levels from baseline to the 22nd day. This study reported significantly lower increase of direct bilirubin levels in the SMOFlipid group compared to the S-LE group (Intralipid). However this study did not provide the data on rate of change of direct bilirubin per week in the two groups.

Death before discharge (outcome 1.14)

Three studies reported data that could be used for the meta-analysis (Analysis 1.14; Larsen 2012; Nehra 2014; Pereira-da-Silva 2017). One study reported no deaths during the study period and that all infants recovered from complications that had occurred during study period (Ariyawangso 2014).

In the subgroup comparison between MOFS-LE and MS-LE, one study reported data with no statistically significant difference between groups (typical RR not estimable; typical RD 0.00, 95% CI -0.08 to 0.08; n = 49; Pereira-da-Silva 2017).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between

groups (typical RR not estimable; typical RD 0.00, 95% CI -0.18 to 0.18; $n = 19$; [Nehra 2014](#)).

In the subgroup comparison between MFS-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR not estimable; typical RD 0.00, 95% CI -0.11 to 0.11; $n = 32$; [Larsen 2012](#)).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR not estimable; typical RD 0.00, 95% CI -0.07 to 0.07; 3 studies; $n = 100$). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$).

Neurodevelopmental outcome (at 6 months and 24 months)

In the subgroup comparison between pure F-LE and S-LE, one study reported data on the neurodevelopmental outcomes using BSID-III, with no statistically significant difference between groups ([Nehra 2014](#)). The authors provided medians and interquartile ranges for cognitive, language and motor scores. The reported P values using non-parametric tests were not significant as per the study report. We did not impute the mean and the SD as this was the only study in the outcome and there was non-parametric distribution.

Alternative LE versus S-LE

Three studies compared alternative-LE versus S-LE ([Angsten 2002](#); [Lima 1988](#); [Magnusson 1997](#)); however, these studies did not contribute to numerical outcomes and are included in the qualitative synthesis.

[Magnusson 1997](#) compared BS-LE (PFE 4501; $n = 10$) versus S-LE ($n = 10$) and reported the fatty acid and carnitine profiles and described biochemical outcomes at and to day five of PN. Both the LE were well tolerated. This short study reported no difference in growth and other biochemical parameters but did not provide data that could be used in analyses. The study reported two infants required treatment for jaundice in the treatment arm, however no comparative figures were provided for the control group.

[Angsten 2002](#) was performed in infants requiring surgery, comparing MS-LE (Vasolipid; 50% MCT and 50% soybean; $n = 10$) versus S-LE (Intralipid; $n = 10$) with regards to lipid, carnitine metabolism and respiratory quotient. This was a short study with description of biochemical and other outcomes at and to day six. Authors described no differences in weight gain. There were no data for the outcomes of our review. The authors mentioned that the plasma glucose concentrations in both groups remained within normal ranges with reference to a graph in the study report that plotted mean values of glucose in both groups. There were no specific data on proportions of hypoglycaemia or hypoglycaemia. The study also described decrease in total and free carnitine in both groups. The triglyceride levels increased in the Vasolipid group and DHA levels decreased in both groups. The respiratory quotient was not different in the two groups.

[Lima 1988](#) ($n = 51$) studied a mixed population of infants with or without surgical conditions, but did not provide the proportion of infants with different conditions and respective results. The mean duration of TPN was 6.8 days (range 3 to 28 days) in MS-LE arm and 9.7 days (range 3 to 34 days) in the LCT arm. The wide range of LE intake was possibly due to the mixed population of infants with surgical and non-surgical conditions including respiratory

conditions. PN duration varied in the study from mean 6.8 (SD 2.5) days (range 3 to 28 days) in the MS-LE group to mean 9.7 (SD 5.5) days (range 3 to 34 days) in the S-LE group due to heterogeneous clinical conditions including infants with surgical conditions in both groups. There were 25% deaths in both arms in this study and study authors reported that none of the deaths were related to PN. This study reported no statistically significant difference in deaths, growth rate or hyperglycaemic events in either arm. Due to the mixed population of surgical and non-surgical infants and non-availability of data by sub-groups we were not able to use the study results.

There were no studies comparing one alternative-LE versus another alternative-LE or one F-LE versus another F-LE.

Term and late preterm infants with cholestasis/PNALD

Infants with cholestasis was a distinct population group considered in this review. There were two eligible studies ($n = 40$) in infants with cholestasis with both studies comparing fish oil-containing LE versus S-LE ([Diamond 2017](#); [Lam 2014](#)). No study compared F-LE versus another F-LE, alternative-LE versus S-LE or one alternative-LE versus another alternative-LE.

Fish oil LE versus non-fish oil LE in infants with cholestasis (Comparison 2)

Resolution of PNALD/cholestasis (conjugated bilirubin less than 2 mg/dL) (outcome 2.1)

We predefined reversal of cholestasis in the review protocol as conjugated bilirubin less than 2 mg/dL due to the effect of intervention ([Kapoor 2018](#)). One randomised study used definition of reversal of cholestasis as conjugated bilirubin less than 2 mg/dL ([Lam 2014](#)). This study found that the cholestasis had resolved in most infants by the trial end point of four months. However, most infants in this study in the S-LE group improved after they were on full enteral intake.

This study also described proportions of infants in both arms who had resolution of cholestasis while on trial PN which was considered for this outcome. There was no statistically significant difference between 10% pure F-LE and 10% S-LE (RR 5.60, 95% CI 0.34 to 93.95; typical RD 0.33, 95% CI -0.01 to 0.67; $n = 16$; [Analysis 2.1](#); very low-quality evidence).

PNALD/cholestasis (any definition) (outcome 2.2)

Two studies ($n = 40$) reported data on cholestasis ([Analysis 2.2](#); [Diamond 2017](#); [Lam 2014](#)). Both studies reported on infants with cholestasis at the end of PN or study end, though the primary outcomes in both studies were different. [Diamond 2017](#) included infants with early hepatic dysfunction ($\text{Cbil} \geq 17 \mu\text{mol/L}$ up to $50 \mu\text{mol/L}$) on two consecutive readings over seven days. This study looked at prevention of progression of PNALD in infants with cholestasis and provided data for infants whose conjugated bilirubin level was greater than $50 \mu\text{mol/L}$ at the study primary end point (Cbil in the week the infant received the last dose of PN, i.e. at 12 weeks, at full enteral tolerance or on development of progressive liver disease).

[Lam 2014](#) included infants with cholestasis defined as conjugated bilirubin $\geq 2 \text{ mg/dL}$. The primary outcome for study by Lam and colleagues was the reversal of PNALD defined as Cbil level less than $34 \mu\text{mol/L}$ (2 mg/dL) within 4 months of the commencement of lipid

treatment. This study also provided information on proportion of infants that recovered from PNAC (or remained cholestatic) while receiving PN.

In the subgroup comparison between MOFS-LE and S-LE, one study reported statistically significantly lesser cholestasis (conjugated bilirubin greater than 50 $\mu\text{mol/L}$) in the MOFS-LE group compared to the S-LE group (typical RR 0.39, 95% CI 0.14 to 1.10; typical RD -0.42, 95% CI -0.78 to -0.06; $n = 24$; [Diamond 2017](#)).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between

groups (RR 0.69, 95% CI 0.43 to 1.13; RD -0.33, 95% CI -0.67 to 0.01; $n = 16$; [Lam 2014](#)).

In the meta-analysis of both subgroups, there was statistically significantly less cholestasis in the F-LE group compared to S-LE group (typical RR 0.54, 95% CI 0.32 to 0.91; typical RD -0.39, 95% CI -0.65 to -0.12; 2 studies; $n = 40$; very low-quality evidence). There was low heterogeneity for RR (24%) and no heterogeneity between the studies for RD (0%). There was no heterogeneity in the test for subgroup differences for RR or RD ($I^2 = 0\%$) ([Figure 3](#)).

Figure 3. Forest plot of comparison: 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, outcome: 2.2 PNALD/cholestasis (any definition).

However, the very low number of participants in this outcome, with different Cbil cut-offs in two included studies, one of which was terminated early, introduced further uncertainty about the outcomes.

Time to resolution of PNALD (outcome 2.3)

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -27.00 days, 95% CI -70.91 to 16.91; $n = 16$; [Analysis 2.3](#); [Lam 2014](#)).

Growth rate (outcome 2.4)

In the subgroup comparison between pure F-LE and S-LE, one study reported data with statistically significant effect in favour of pure F-LE compared to S-LE (MD 45.00 g/week, 95% CI 15.00 to 75.00; $n = 16$; [Analysis 2.4](#); very low-quality evidence; [Lam 2014](#)). It is worth noting that [Lam 2014](#) used 10% Intralipid (S-LE) preparation which is no longer recommended.

Head growth velocity (outcome 2.5)

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups. The study authors reported the data as mean and 95% CIs and we imputed the SD using a normal distribution (rather than t distribution) to get similar results to the study authors (MD 0.16 cm/week, 95% CI -0.01 to 0.33; $n = 16$; $P = 0.06$; [Analysis 2.5](#); [Lam 2014](#)).

Any sepsis (clinical or culture positive (or both)) (outcome 2.6)

Two studies ($n = 40$) reported data in a format that could be used for the meta-analysis and specific definitions for sepsis were not provided in the study reports ([Analysis 2.6](#); [Diamond 2017](#); [Lam 2014](#)).

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 1.48, 95% CI 0.52 to 4.18; typical RD 0.15, 95% CI -0.24 to 0.53; $n = 24$; [Diamond 2017](#)).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 0.78, 95% CI 0.14 to 4.23; typical RD -0.06, 95% CI -0.49 to 0.37; $n = 16$; [Lam 2014](#)).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR 1.21, 95% CI 0.50 to 2.92; typical RD 0.06, 95% CI -0.23 to 0.35; 2 studies; $n = 40$; very low-quality evidence). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$).

Hypertriglyceridaemia (outcome 2.7)

In the subgroup comparison between MOFS-LE and S-LE, one study reported data for this outcome. The report mentioned hyperlipidaemia. No definition was provided. There was no statistically significant difference between groups (typical RR 0.79,

95% CI 0.30 to 2.09; typical RD -0.1, 95% CI -0.49 to 0.29; n = 24; very low-quality evidence; [Analysis 2.8](#); [Diamond 2017](#)).

Hyperglycaemia (outcome 2.8)

One study reported data on hyperglycaemia with no statistically significant difference between groups. No definition was provided (typical RR 1.48, 95% CI 0.52 to 4.18; typical RD 0.15, 95% CI -0.24 to 0.53; n = 24; [Analysis 2.8](#); [Diamond 2017](#)).

Conjugated bilirubin levels (outcome 2.9)

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with statistically significant effect in favour of MOFS-LE with lower Cbil values compared to S-LE excluding an outlier in the data who had significant increase in the level of conjugated bilirubin with sepsis (MD -47.00 µmol/L, 95% CI -71.65, -22.35; n = 24; [Analysis 2.9](#); low-quality evidence; [Diamond 2017](#)). The study authors reported data in mean and 95% CI (as confirmed by the study author) for the distribution excluding the outlier. There was no statistically significant difference between groups when the outlier was included in the analysis. Study authors also performed analysis by including the conjugated bilirubin value for the outlying participant when the participant had improved and this analysis showed a statistically significant difference between groups.

In their study report the authors defined cholestasis as increased conjugated bilirubin levels not related to sepsis. Therefore, we presented the data without the outlier and described the analytical aspects reported by the study.

Gamma-glutamyltransferase levels (outcome 2.10)

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with statistically significant effect in favour of S-LE (MD 115.00 IU/L, 95% CI 12.86 to 217.14; n = 24; [Analysis 2.10](#); [Diamond 2017](#)). Diamond and colleagues interestingly found significantly higher GGT despite a trend towards lower ALP in the SMOFlipid group which the study authors could not explain.

Alanine aminotransferase levels (outcome 2.11)

In the subgroup comparison between MOFS-LE and S-LE, one study ([Diamond 2017](#)) (MOFS-LE versus S-LE; n = 24) reported data with no statistically significant difference between groups (MD -36.00 IU/L, 95% CI -155.41 to 83.41; n = 24; [Analysis 2.11](#); [Diamond 2017](#)).

Alkaline phosphatase levels (outcome 2.12)

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -119.00 IU/L, 95% CI -240.01 to 2.01; n = 24; [Analysis 2.12](#); [Diamond 2017](#)).

Triglyceride levels (outcome 2.13)

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (MD -0.40 mmol/L, 95% CI -0.85 to 0.05; n = 16; [Analysis 2.13](#); [Lam 2014](#)). Test of heterogeneity was not applicable in the subgroup. No meta-analysis was possible.

Rate of change of alanine aminotransferase (outcome 2.14)

In the subgroup comparison between pure F-LE and S-LE, one study reported statistically significantly lower rate of increase of ALT in the pure F-LE group (1.1 IU/L/week, 95% CI -5.2 to 7.5 versus 9.1 IU/L/

week, 95% CI 4.1 to 14.1; P = 0.02; MD -8.00 IU/L/week, 95% CI -14.79 to -1.21; n = 16; [Analysis 2.14](#); [Lam 2014](#)).

Rate of change of conjugated bilirubin (outcome 2.15)

In the subgroup comparison between pure F-LE and S-LE, one study reported statistically significantly lower rate of increase of conjugated bilirubin in the pure F-LE group (0.6 µmol/L/week, 95% CI -9.5 to 10.8 with pure F-LE versus 13.5 µmol/L/week, 95% CI 5.4 to 21.6 with S-LE; P = 0.03; MD -12.9 µmol/L/week, 95% CI -23.69 to -2.11; n = 16; very low-quality evidence; [Analysis 2.15](#); [Lam 2014](#)).

Death before discharge (outcome 2.16)

Two studies (n = 40) reported data with no study individually reporting any significant difference between the two groups ([Analysis 2.16](#); [Diamond 2017](#); [Lam 2014](#)). However, all the deaths in both studies were complicated or due to progressive liver disease.

In the subgroup comparison between MOFS-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 0.39, 95% CI 0.02 to 8.69; typical RD -0.08, 95% CI -0.27 to 0.12; n = 24; [Diamond 2017](#)).

In the subgroup comparison between pure F-LE and S-LE, one study reported data with no statistically significant difference between groups (typical RR 0.16, 95% CI 0.01 to 2.88; typical RD -0.29, 95% CI -0.63 to 0.06; n = 16; [Lam 2014](#)).

In the meta-analysis of all subgroups, there was no statistically significant difference between groups in the meta-analysis (typical RR 0.24, 95% CI 0.03 to 1.87; typical RD -0.16, 95% CI -0.36 to 0.04; 2 studies; n = 40; very low-quality evidence). There was no heterogeneity among the subgroups for RR or RD ($I^2 = 0\%$) or for subgroup differences in RD (4.2%).

No study reported on outcomes of body composition, jaundice requiring treatment, phototherapy duration, duration of supplemental oxygen, home oxygen therapy, thrombocytopenia, time to development of PNALD, EFA deficiency or need for liver transplantation in infants with surgical conditions or infants with PNALD/cholestasis.

DISCUSSION

This review synthesised the current evidence in late term and preterm infants regarding the use of LEs in PN. The PN in this group of infants has very different indications compared to preterm infants. The most common group of infants requiring PN in the late preterm and term group of infants are those who have an underlying surgical condition. Another group of infants often with surgical conditions who require PN are those infants who have developed PNALD/cholestasis.

This review aimed to synthesise the evidence in three predefined population groups: late preterm and term infants:

- without surgical conditions or cholestasis;
- with surgical conditions or
- who had developed PNALD/cholestasis.

There were no restrictions on comorbidities including surgery in infants with PNALD.

LE were classified in three broad groups:

- all fish oil-containing LE including pure fish oil (pure F-LE) and multi-source LE (e.g. MCT-olive-fish-soybean oil-LE (MOFS-LE), MCT-fish-soybean oil-LE (MFS-LE) and olive-fish-soybean-LE (OFS-LE));
- conventional pure soybean-LE (S-LE);
- alternative LE (e.g. MCT-soy-LE (MS-LE), Olive-soy-LE (OS-LE) and borage oil based LE).

We considered four broad comparison groups including all possible pair-wise LE subgroup comparisons as follows.

- Fish oil LE versus non-fish oil LEs (6 studies; n = 182):
 - * MOFS-LE versus S-LE (2 studies; n = 66);
 - * MOFS-LE versus MS-LE (1 study; n = 49);
 - * MFS-LE versus S-LE (1 study; n = 32);
 - * Pure F-LE versus S-LE (2 studies; n = 35).
- Fish oil LE versus another fish oil LE: (no studies).
- Alternative LE versus S-LE (3 studies; n = 91):
 - * MS-LE versus S-LE (2 studies; n = 71);
 - * BS-LE versus S-LE (1 study; n = 20).
- Alternative LE versus another alternative LE (no studies).

Two studies (n = 40) were performed in infants with PNALD/cholestasis including one (Diamond 2017; n = 24) that compared MOFS-LE (SMOFlipid) versus S-LE (Intralipid), and the other (Lam 2014; n = 16) compared pure F-LE (Omegaven) versus S-LE (Intralipid). All other studies (7 studies; n = 233) were performed in infants with surgical conditions or mixed surgical and non-surgical populations. No study was identified in late preterm and term infants without surgical conditions or cholestasis.

There was wide variation in gestation and weight at birth in the included studies, often with mixed gestations including term and preterm infants.

The studies included in this review were performed in seven different countries including two in Sweden; two in Canada; and one each in Thailand, Hong Kong, the UK, the USA and Portugal.

Summary of main results

The review included nine randomised studies (n = 273). However, the data were limited to six studies (n = 182). All four studies in surgical infants (n = 142) that contributed data to the review included participants that did not have pre-existing PNALD. Both studies in the infants with pre-existing PNALD (2 studies; n = 40) had mostly infants with underlying surgical conditions as study participants.

GRADE quality ranged from low to very low for all comparisons as the included studies were small single-centre studies with limited sample size. Three of six studies that contributed data for the review were terminated early for various reasons.

There are several potential advantages with the fish oil-based LEs. In observational studies, a pure F-LE (Omegaven) decreased and even reversed PNALD in infants, resulting in decreased mortality and lower levels of triglycerides, Cbil and liver enzymes compared with S-LE (20% Intralipid) (de Meijer 2009; Puder 2009). One systematic review in preterm infants suggested evidence of significant benefit of fish oil in reversing PNALD; however, the

evidence was synthesised from randomised and non-randomised studies (Park 2015).

In the primary outcomes of the review, we defined PNALD/cholestasis with Cbil levels 2 mg/dL or greater and the resolution of PNALD/cholestasis as decrease in Cbil less than 2 mg/dL. We applied no restrictions on the time of detection or time of resolution of PNALD due to no standard reporting protocols.

There was heterogeneity in definitions for PNALD/cholestasis used by the included studies. The included studies reported proportion of infants with cholestasis with Cbil levels ranging from 17.1 µmol/L (1 mg/dL) to 50 µmol/L (about 3 mg/dL). The timing of cholestasis detection and performance of liver function tests varied between studies.

Two studies reported PNALD outcomes using the same Cbil cut-off levels as predefined in the current review (i.e. 2 mg/dL). Nehra 2013 (infants with surgical conditions) and Lam 2014 (16 infants with cholestasis) compared a pure F-LE (Omegaven) versus S-LE (Intralipid) showing no evidence of difference in the incidence (Nehra 2013) or resolution (Lam 2014) of PNALD. The study by Nehra and colleagues used 1 g/kg/day of LE in both arms. This study was terminated early after an interim analysis due to the low cholestasis rates in study participants with only one infant in each arm developing cholestasis over the study period of two years.

We also considered an outcome allowing for any definition of PNALD (different Cbil cut-off levels). In a meta-analysis for PNALD/cholestasis using any definition, there was no evidence of difference in incidence of cholestasis in infants with surgical conditions (without pre-existing PNALD) using fish oil LE versus non-fish oil LE (typical RR 1.20, 95% CI 0.38 to 3.76; typical RD 0.03, 95% CI -0.14 to 0.20; 2 studies, n = 68; low-quality evidence).

There was a paucity of studies in infants with cholestasis with only two small studies reporting on outcomes related to cholestasis comparing fish oil versus non-fish oil LE (Diamond 2017; Lam 2014). Lam 2014 compared 10% Omegaven versus 10% Intralipid in infants with PNALD/cholestasis (defined as Cbil greater than 34 µmol/L). The primary outcome for the study was the reversal of PNALD defined as Cbil less than 34 µmol/L (2 mg/dL) within four months of the commencement of lipid treatment. This study also reported data on the proportion of infants who recovered from PNALD (or remained cholestatic) while receiving PN. Diamond 2017 compared SMOFlipid versus Intralipid in infants with early hepatic dysfunction (Cbil 17 µmol/L to 50 µmol/L; n = 24) and evaluated prevention of progression of PNALD with use of fish oil LE. Diamond 2017 reported the proportion of infants with Cbil greater than 50 µmol/L in the two arms, at the study end point (the week the infant received the last dose of PN, i.e. at 12 weeks, at full enteral tolerance or at the development of progressive liver disease). In infants with PNALD/cholestasis using any Cbil cutoff, the meta-analysis showed evidence of lesser cholestasis in the fish oil-LE group versus S-LE (typical RR 0.54, 95% CI 0.32 to 0.91; typical RD -0.39, 95% CI -0.65 to -0.12; NNTB 3, 95% CI 2 to 9; 2 studies; n = 40; very low-quality evidence) (Figure 3). However, the very low number of participants in this outcome, with different Cbil cut-offs in two included studies, one of which was terminated early and heterogeneity in study methodology, introduced further uncertainty about the outcomes.

In the primary outcome of growth, in the infants with underlying surgical conditions, no study reported any differences in growth

parameters in the fish oil versus non-fish oil LE group (data were not available for meta-analysis). One study in infants with cholestasis reported evidence of significantly more weight gain in the fish oil group (45 g/week, 95% CI 15.00 to 75.00; $n = 16$; very low-quality evidence; [Lam 2014](#)).

In the secondary outcomes of the review, one study in surgical infants reported statistically significantly lower Cbil levels in fish oil LE group (MD $-33.52 \mu\text{mol/L}$, 95% CI -50.60 to -16.44 ; [Ariyawangso 2014](#)). This was an open-label randomised study that did not report Cbil for 42% of the enrolled infants. [Ariyawangso 2014](#) reported a (four times) higher mean level of Cbil in the S-LE group (Intralipid; 2.54 (SD 1.75) mg/dL) compared to fish oil group (SMOFlipid; 0.58 (SD 0.52) mg/dL) with no evidence of differences in the other liver enzymes. The other study in this outcome showed no evidence of difference in the conjugated bilirubin levels between groups (MD $0.0 \mu\text{mol/L}$, 95% CI -11.3 to 11.30 ; [Nehra 2014](#)). There was high heterogeneity between the studies ($I^2 = 90\%$). Therefore, we did not perform a meta-analysis and presented the results of both studies separately.

One study in infants with cholestasis comparing MOFS-LE versus S-LE reported statistically significantly lower Cbil levels in the MOFS-LE group compared with S-LE group (MD $-47.00 \mu\text{mol/L}$, 95% CI -71.65 to -22.35 ; $n = 24$) while excluding an infant who had sepsis-related worsening of Cbil ([Diamond 2017](#)). Authors also reported a second analysis including the four weeks' conjugated bilirubin value for that infant. However, authors could not explain the contradictory finding of significantly higher GGT levels in the MOFS-LE group in this study. There were no differences in the mean levels of ALP or ALT in both groups in this study.

One small study in infants with cholestasis reported statistically significantly lower rates of rise in ALT and Cbil in infants receiving a 10% pure F-LE (Omegaven) compared to a 10% soy LE (ALT: -8.00 U/L/week , 95% CI -14.79 to -1.21 ; Cbil: $-12.90 \mu\text{mol/L/week}$, 95% CI -23.69 to -2.11 ; $n = 16$; [Lam 2014](#)).

There was no evidence of differences in ventilation duration, NEC and biochemical parameters including GGT, ALT and ALP levels between the fish oil LE and non-fish LE in infants with surgical conditions.

In the outcome of hypertriglyceridaemia, one study in infants with surgical conditions reported significantly less hypertriglyceridaemia with fish oil LE (typical RR 0.25, 95% CI 0.06 to 1.01; typical RD -0.28 , 95% CI -0.50 to -0.06 ; $n = 49$; [Pereira-da-Silva 2017](#)). However, one other study did not report hypertriglyceridaemia in either groups ([Nehra 2014](#)). There was high heterogeneity in the outcome for RD ($I^2 = 81\%$ for between-study heterogeneity, 73% for subgroup differences). Therefore, we did not perform a meta-analysis and described the results of both studies separately.

[Lam 2014](#) reported two deaths in the 10% Intralipid group due to hepatic and multiorgan failure compared to no deaths in the 10% fish oil group, though the difference was not statistically significant. There was no evidence of differences in death, sepsis and mean triglyceride levels in infants with surgical conditions or cholestasis (very low-quality evidence).

One study in infants with surgical conditions ($n = 11$) reported neurodevelopmental assessment outcomes, showing no difference

between groups at six and 24 months. Another study in infants with cholestasis ($n = 16$) reported no difference in the head growth.

No studies reported IHCL content, EFA deficiency and the need for liver transplantation.

Overall completeness and applicability of evidence

The evidence presented in this review was significantly limited by a paucity of randomised studies reporting on clinically important outcomes including PNALD. The included studies had very limited sample size.

We did not have data for sub-group analysis based on gestational age, lipid dosing or continuous versus intermittent infusion.

Quality of the evidence

The quality of evidence in this review ranged from low to very low for most of the outcomes (GRADE Working Group recommendations; [Schünemann 2013](#)). This was primarily due to optimal information size not being achieved, with wide CIs for most of the outcomes. The studies included in this review were mostly small single center studies, that used different definitions of cholestasis and had heterogeneity in methodology and reporting of outcomes including PNALD. Evidence was further downgraded due to early termination in some studies. Heterogeneity was not applicable in presence of a single study in an outcome ([Appendix 6](#)).

Potential biases in the review process

Publication bias was difficult to evaluate as there were few studies in any of the outcomes. The evidence synthesis results could be biased in the presence of a few small significant studies with study-level biases.

Three out of six studies that contributed data to this review were terminated early, which may be another source of bias.

Agreements and disagreements with other studies or reviews

In the current review, we only included randomised studies whereas some previous reviews have included randomised and non-randomised studies ([Park 2015](#)). Due to the presence of non-randomised studies, which could have exaggerated the effect sizes, there is a possibility that the effect sizes reported by the previous reviews may have overestimated the effect of fish oil-based LEs. However, for the same reason (including only randomised studies), the current review was limited by very small numbers in each comparison.

AUTHORS' CONCLUSIONS

Implications for practice

This review explores the evidence regarding the potential benefits of different lipid emulsions (LEs) including fish oil-containing LEs in term and late preterm infants with or without surgical conditions or cholestasis. Though there is suggestion of less cholestasis with fish oil LE compared with soy bean-based LE in infants with PNALD, the evidence is of very low quality and limited by the very small number of participants from two small studies with methodological differences, one of which was terminated early.

Based on the current review, there exists insufficient data from randomised studies to determine with any certainty, the potential benefit of any LE including fish oil-containing LEs over another LE, for prevention or resolution of cholestasis or any other outcomes in term and late preterm infants with underlying surgical conditions or cholestasis. We found no studies in infants without surgical conditions or cholestasis.

Currently there is paucity of good-quality evidence to make any recommendations and further research in this field is warranted.

Implications for research

Parenteral nutrition-associated liver disease (PNALD) is one of the most important morbidities afflicting infants and children with

long-term parenteral nutrition and can cause significant adverse outcomes including progressive liver disease and death.

Further research is warranted to establish the role of fish oil and lipids from other sources, and to define the ideal proportions of individual lipid constituents in infants with cholestasis or infants on long-term parenteral nutrition. It is not currently known whether there are any mid-term or long-term effects on growth and neurodevelopment with different types and proportions of lipids constituents in LEs.

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Waitzberg DL, Torrinhas RS, Jacintho TM. New parenteral lipid emulsions for clinical use. *Journal of Parenteral and Enteral Nutrition* 2006;**30**(4):351-67. [DOI: [10.1177/0148607106030004351](https://doi.org/10.1177/0148607106030004351); PUBMED: 16804134]

Wanten 2007

Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. *American Journal of Clinical Nutrition* 2007;**85**(5):1171-84. [DOI: [10.1093/ajcn/85.5.1171](https://doi.org/10.1093/ajcn/85.5.1171); PUBMED: 17490951]

Xu 2012

Xu ZW, Li YS. Pathogenesis and treatment of parenteral nutrition-associated liver disease. *Hepatobiliary & Pancreatic Diseases International* 2012;**11**(6):586-93. [PUBMED: 23232629]

References to other published versions of this review

Kapoor 2018

Kapoor V, Malviya MN, Soll R. Lipid emulsions for parenterally fed preterm infants. *Cochrane Database of Systematic Reviews* 2018, Issue 11. [DOI: [10.1002/14651858.CD013163](https://doi.org/10.1002/14651858.CD013163)]

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Angsten 2002

Methods	Design: double-blind, randomised trial
	Setting: Department of Paediatric Surgery, University Children's Hospital, SE-751 85 Uppsala, Sweden
	Study enrolment: not mentioned
	I. Allocation concealment: could not determine
	II. Blinding of intervention: could not determine
	III. Blinding of outcome measurement(s): could not determine
	IV. Complete follow-up: yes
Participants	Inclusion criteria: neonates of both sexes with gestational age 36–41 weeks at birth, birthweight 2.5–4.0 kg and postnatal age of up to 4 days, needing surgical treatment and requiring TPN for ≤ 5 days. Neonates needing surgery for various oesophago-gastrointestinal malformations were assigned before surgery.

Angsten 2002 (Continued)

Exclusion criteria: metabolic disease, renal disease, inflammatory disease, septic syndrome or haematological disorder. The neonates should not have been receiving treatment with catecholamines or have any known malignancy.

Interventions	<p>20 neonates</p> <p>Group 1 (n = 10): MS-LE; Vasolipid, containing 50% MCT and 50% LCT</p> <p>Group 2 (n = 10): S-LE; Intralipid</p> <p>Total amount of lipid infused on the first day was 2 g/kg/day, which was increased at a daily rate of 0.5 g/kg/day until an infusion rate of 3 g/kg/day was reached. Before the start of TPN, after 5 days of TPN and 5 hours after the lipid infusion ended, 2 blood samples (2.5 mL) were taken for measurement of free and total plasma carnitine concentrations, free fatty acids, fatty acid composition of plasma cholesterol esters, phospholipids, triglycerides and ketones as b-hydroxybutyrate. A sample of adipose tissue weighing approximately 15 mg and a sample of muscle weighing approximately 30 mg were taken during surgery as an open biopsy with a scalpel.</p>
Outcomes	<p>Primary outcomes: fatty acid compositions in plasma and adipose tissue and carnitine concentrations in plasma and muscle. Secondary outcomes: heart rate, body temperature, bodyweight and clinical symptoms recorded daily. Haematological (haemoglobin, leukocytes and platelets) and biochemical (aspartate aminotransferase, ALT, sodium, potassium, creatinine, alkaline phosphatase, albumin and bilirubin) parameters measured on day 0, just before the first infusion of TPN started and after termination of study.</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "double blind randomized manner."</p> <p>Comment: random sequence generation not described.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "assigned before surgery in a double blind randomized manner."</p> <p>Comment: not described.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Comment: unclear risk for blinding (not described).</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Comment: no blinding but outcomes were objective; therefore, low material risk.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: no concerns.</p>
Selective reporting (reporting bias)	Unclear risk	<p>Comment: protocol not available so no judgement possible.</p>
Other bias	Low risk	<p>Not identified.</p>

Ariyawangso 2014

Methods	Design: prospective, open-label, randomised study in surgical neonates Setting: Queen Sirikit National Institute of Child Health, Bangkok, Thailand Study enrolment: 1 March 2013 and 30 November 2013 I. Allocation concealment: no II. Blinding of intervention: no III. Blinding of outcome measurement(s): no IV. Complete follow-up: no
Participants	Surgical neonates with gastroschisis, omphalocele, jejuno-ileal atresia or duodenal atresia requiring PN for ≥ 7 consecutive days were eligible to participate in the study. Infants were excluded if they had already received PN; or had Down's syndrome, severe congenital malformations, PDA, anuria due to circulation failure, liver/haemolytic diseases, hepatitis, thrombocytopenia, HIV, oxygen saturation $< 80\%$ for > 2 hours, severe acidosis, application of catecholamines, multiorgan failure, hypoxic-ischaemic encephalopathy, shock and sepsis.
Interventions	42 surgical infants requiring PN Group 1 (n = 21): MOFS-LE; SMOFlipid 20% Group 2 (n = 21): S-LE; Intralipid 20% LE started parenterally at 0.5 g/kg/day on day 1 and increased by increments of 0.5 g/kg/day daily up to 3 g/kg/day for term and 3.5 g/kg/day preterm neonates, until it reached 50% of total energy intake. Blood samples were collected for assessment of primary and secondary outcomes on day 0, 8, 15 and 22 of the study if PN was continued.
Outcomes	Primary outcomes: safety outcomes including liver enzymes ALT, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, total bilirubin, conjugated bilirubin, lipid profile, blood urea nitrogen, serum creatinine and haematological parameters Secondary outcomes: efficacy outcomes including infant's weight, head circumference and length at study entry and exit
Notes	
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Unclear risk Quote: "randomised 1:1 by block size 4." Comment: authors did not describe the method to attain the random component. By consensus, we allocated an unclear risk score for this bias category.
Allocation concealment (selection bias)	High risk Comment: authors did not describe the measures taken for allocation concealment. Also blocked designs can be at risk especially in open-label study as at times it may be possible to guess the blocks unless specific measures are taken.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk Quote: "Open label randomised study in surgical newborns." Comment: design increased risk of performance bias; however, most outcomes were objective so the risk may have been lower. Unclear risk of bias by review author consensus.

Ariyawangso 2014 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Open label randomized study in surgical newborns." Comment: most outcomes were objective based on blood investigations. Therefore, the impact on the objective outcomes would be low. However, some of the outcomes such as head circumference with more interobserver differences may have been impacted. We assigned unclear risk of bias by re-view author consensus.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "On day 22 of the study, there were 24 surgical neonates remaining in the study (n = 13 in the control group and n = 11 in the experimental group) as 18 neonates (n = 8 in the control group and n = 10 in the experimental group) had recovered." Comment: out of 42 infants in the study population, safety and efficacy data presented for 24. Data were not included for about 40% of infants. Though this was balanced in both arms, this may have introduced bias depending on underlying bilirubin distribution due to large percentages.
Selective reporting (reporting bias)	Unclear risk	Study protocol not available.
Other bias	Low risk	Not identified.

Diamond 2017

Methods	<p>Design: multicentre blind randomised trial in 26 preterm infants</p> <p>Setting: NICUs at multiple sites including Hospital for Sick Children, Toronto, ON, Canada; McMaster Children's Hospital, Hamilton, ON, Canada; Alberta Children's Hospital, Calgary, AB, Canada; Stollery Children's Hospital, Edmonton, AB, Canada; and CHU Sainte-Justine, Montreal, QC, Canada</p> <p>Study enrolment: January 2009 to September 2011</p> <p>I. Allocation concealment: yes</p> <p>II. Blinding of intervention: yes</p> <p>III. Blinding of outcome measurement(s): possibly yes, low risk</p> <p>IV. Complete follow-up: yes</p>
Participants	<p>Population: infants with hepatic dysfunction due to surgical conditions</p> <p>Inclusion criteria: infants aged < 24 months with short bowel syndrome or intestinal failure who received substantial PN support (> 40% total calories) and were demonstrating early hepatic dysfunction (Cbil 17–50 µmol/L (1–3 mg/dL)) in the absence of sepsis. Although the age of inclusion was < 24 months, all the included infants were in preterm or borderline preterm range with the outer range of the ages being < 6 months and therefore met the current review's inclusion criteria.</p> <p>Age, mean (range): 6.5 (4.3 to 8.7) weeks in SMOFlipid group vs 5.3 (3.5 to 7.2) weeks in Intralipid group</p> <p>Gestational age, mean (range): 34.5 (32.4 to 36.7) weeks in SMOFlipid group vs 35.2 (33.2 to 37.1) weeks in Intralipid group</p> <p>Exclusion criteria: sepsis or haemodynamic instability of any cause; coagulopathy (platelets ≤ 150,000/µL, or INR ≥ 1.4); hypersensitivity to fish-, egg- or soybean protein or to any of the active substances or excipients; current enrolment in another clinical trial involving a surgical or pharmacological intervention; serum Cbil > 50 µmol/L; hyperlipidaemia; treatment with intravenous N-acetylcysteine or oral ursodeoxycholic acid; renal insufficiency; disorders of fluid balance; unstable medical conditions</p>

Diamond 2017 (Continued)

Interventions	<p>26 infants randomised; results available for 24 infants (11 infants in SMOFlipid group; 13 in Intralipid group)</p> <p>Group 1 (n = 11): MOFS-LE; SMOFlipid</p> <p>Group 2 (n = 13): S-LE; Intralipid</p> <p>TPN protocol: participants received trial lipid for up to 12 weeks. Participants also ended the trial if they achieved full enteral tolerance (autonomy from PN) prior to this time point or if they developed progressive liver disease defined by a serum Cbil > 100 µmol/L for > 14 days. Lipid dosing was according to a nomogram which adjusted the amount of the lipids proportional to the enteral intake. All type of enteral formulas were allowed except the enteral fish oil solution.</p>
Outcomes	<p>Primary outcome: last value of the Cbil the week the child received the last dose of the trial lipid (i.e. at 12 weeks, at full enteral tolerance or on the development of the progressive liver disease)</p> <p>Secondary outcomes: other liver markers in the blood measured; weight, length and head circumference were assessed at baseline, week 6 and post-trial. A complete blood count was done at weeks 0, 4 and 8, and post-trial. An INR, C-reactive protein, immunological markers (interleukins 1, 6, 8, 10 and 12; TNF-α), nephelometry, serum cholesterol and serum triglycerides were assessed at baseline, week 6 and post-trial. Red blood cell phospholipid composition was assessed at baseline, week 6 and post-trial.</p>
Notes	<p>Investigators had a provision of replacement of the study participants who discontinued the PN prior to second week of the study due to achievement of full enteral tolerance.</p> <p>Patients who received SMOFlipid were more likely to have a decrease in serum Cbil to 0 µmol/L than those in the Intralipid group over the entire observation period (HR 10.6, 95% CI 1.3 to 86.9; P = 0.006).</p> <p>At the time the primary end point was achieved, 3 (27%) infants in the SMOFlipid group had a serum Cbil > 50 µmol/L, while 9 (69%) infants in the Intralipid group had a Cbil > 50 µmol/L (P = 0.04).</p> <p>The authors did not provide specific definitions for some adverse outcomes, e.g. sepsis. Beginning and end weights were described and growth rates could not be derived due to lack of data on covariance.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "The randomisation sequence was developed by the research support pharmacy using a random number table prior to enrolment of the first patient. The sequence was developed in blocks of variable size without investigator input or knowledge."</p> <p>Comment: done.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Allocation concealment was achieved by the randomisation sequence only being known to the research support pharmacy at the Hospital for Sick Children. The group assignment was relayed to the dispensing pharmacist at the patient's institution only after enrolment had occurred."</p> <p>Comment: done.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "All participants, treating clinicians, and investigators were blinded to the treatment assignment. Only the research support pharmacist at the Hospital for Sick Children and the dispensing pharmacist at the patient's institution were aware of the group assignment."</p> <p>Comment: possibly done and low risk for the objective outcomes.</p>

Diamond 2017 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All participants, treating clinicians, and investigators were blinded to the treatment assignment. Only the research support pharmacist at the Hospital for Sick Children and the dispensing pharmacist at the patient's institution were aware of the group assignment." Comment: possibly done and low risk for the objective outcomes.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Complete outcomes reported." 2 infants in the SMOFlipid arm were not analysed as they achieved full enteral feeding within 14 days. However, as this was less than 20% of the data it may not have made a significant difference (author consensus). Comment: done.
Selective reporting (reporting bias)	Low risk	Quote: "This trial was registered at clinicaltrials.gov as NCT00793195." Comment: no significant concerns as per the outcome reporting.
Other bias	Low risk	Comment: None identified.

Lam 2014

Methods	Design: single-centre study Setting: Departments of Paediatrics, Paediatric Surgery and Pharmacy at the Prince of Wales Hospital, Sha Tin, Hong Kong Study enrolment: September 2005 to December 2009 I. Allocation concealment: yes II. Blinding of intervention: yes III. Blinding of outcome measurement(s): yes IV. Complete follow-up: yes
Participants	Inclusion criteria: infants who developed PNAC and fulfilled the inclusion criteria: Cbil ≥ 34 $\mu\text{mol/L}$ (2 mg/dL), expected to continue requiring PN for > 2 weeks and informed parental consent. Exclusion criteria: major congenital or lethal chromosomal abnormalities; multiorgan failure or imminent death; and cholestatic jaundice secondary to other known causes, e.g. congenital or acquired TORCH (acronym for a group of diseases that cause congenital conditions; Toxoplasmosis, Other (such as syphilis, varicella, mumps, parvovirus and HIV), Rubella, Cytomegalovirus, Herpes simplex), syphilis, hepatitis B or C infection, biliary atresia or other intra- or extrahepatic diseases obstructing bile flow.
Interventions	Group 1 (n = 9): pure F-LE; 10% Omegaven (Fresenius-Kabi AG, Bad Homburg vor der Höhe, Germany) Group 2 (n = 7): S-LE; 10% Intralipid (Fresenius-Kabi AG, Uppsala, Sweden)
Outcomes	Primary outcome: reversal of PNAC, defined as Cbil < 34 $\mu\text{mol/L}$ within 4 months after commencement of lipid treatment Secondary outcomes: rate of change of weekly liver function tests, infant growth parameters (head circumference and bodyweight), blood lipid profile and number of episodes of late-onset infection
Notes	Pharmacists not involved in the care of the infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period.

Lam 2014 (Continued)

There were 2 deaths in the S-LE group with both infants dying of hepatic and multiorgan failure secondary to septicaemia.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Pharmacists not involved in the care of the infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period."</p> <p>From appendix: "Randomisation was performed by the computer minimising three predetermined clinical parameters with equal weighting that could potentially influence the outcome measures."</p> <p>Comment: done with details in appendix.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Pharmacists not involved in the care of the infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period."</p> <p>Comment: done with details in appendix.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Pharmacists not involved in the care of the infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period."</p> <p>From appendix: "For infants randomised to the soy-based parenteral lipid preparation (SLP) arm, the preparation used was not only identical to FOLP in appearance, but also volume prescribed and delivered."</p> <p>Comment: probably done with details in appendix.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Pharmacists not involved in the care of the infants prepared the lipids and the clinical and research teams were unaware of the randomisation during the study period."</p> <p>Comment: probably done with details in appendix.</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "No concerns."</p> <p>Comment: low risk.</p>
Selective reporting (reporting bias)	Low risk	<p>Quote: "Chinese Clinical Trial Registry: ChiCTR-TRC-09000718."</p> <p>Comment: on the registry, trial number was ChiCTR-TRC-08000717.</p> <p>Comment: low risk.</p>
Other bias	Unclear risk	<p>Quote: the study was stopped as "parents became unwilling for randomisation."</p> <p>Comment: unclear risk as the trial was stopped mid-way due to unwillingness of parents.</p>

Larsen 2012

Methods Design: double-blind, randomised, controlled clinical trial

Larsen 2012 (Continued)

Setting: Stollery Children's Hospital, Edmonton, AB, Canada

I. Allocation concealment: yes

II. Blinding of intervention: yes

III. Blinding of outcome measurement(s): yes

IV. Complete follow-up: yes

Participants	Infants scheduled to have open heart surgery with following criteria: appropriate-for-gestational-age; Apgar scores > 7 at 5 and 10 minutes; and no clinical or microbiological evidence of infection preoperatively to receive 1 of 2 intravenous lipid preparations: the control group received an emulsion composed exclusively of LCTs from soybean oil (Intralipid; Clintec Nutrition Company, Baxter, Deerfield, IL, USA), while the treatment group received an emulsion containing 50% MCTs and 40% LCTs from soybean oil and 10% fish oil (MLF 541, Lipoplus; B Braun Melsungen, Melsungen, Germany). Infants receiving immunosuppressive or anti-inflammatory drugs (e.g. indomethacin, aspirin) were excluded.
Interventions	32 infants undergoing cardiopulmonary bypass and dependent on PN were randomised: Group 1 (n = 16): MFS-LE; Lipidem (50:40:10 mixture of MCT, soybean oil and fish oil; MLF 541, Lipoplus; B Braun Melsungen, Melsungen, Germany) Group 2 (n = 16): S-LE; Intralipid (Clintec Nutrition Company, Baxter, Deerfield, IL, USA) PN was administered for 3 days (1 to 4 days) preoperatively and 10 days postoperatively.
Outcomes	Fatty acids (EPA, AA, LA, DHA), lymphocytes, granulocyte macrophage-colony stimulating factor (GM-CSF) and inflammatory markers were quantified at baseline; before surgery; and days 1, 7 and 10 after surgery. The measured inflammatory markers included: leukotriene B4, (TNF)-α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8 and IL-10 interferon-gamma.
Notes	Results for the fatty acids, lymphocyte concentrations and procalcitonin from the study were published in Larsen and colleagues' 2015 article "Pretreatment with an Intravenous lipid emulsion increases plasma eicosapentanoic acid and downregulates leukotriene B4, procalcitonin, and lymphocyte concentrations after open heart surgery in infants" J Parenter Enteral Nutr. 2015 Feb;39(2):171-9. The baseline characteristics of study participants reported in both study reports were identical. The 2015 study report references the study report published by the authors in 2012 "The current study expanded on the previous results" and "The study used the same methodology described previously".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The hospital pharmacy research office generated the randomisation sequence via computer in blocks of eight, using an allocation ratio of 1:1." Comment: low risk.
Allocation concealment (selection bias)	Low risk	Quote: "As infants were enrolled in the study by the principal investigator they were randomised by pharmacy staff to receive one of two intravenous lipid preparations according to the computer-generated allocation sequence." Comment: low risk.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Pharmacy was involved in the preparation of the coded syringes which were labelled by pharmacy with codes only known to the pharmacy." "Parents, guardians, study personnel and attending staff remained blinded to treatment until after data analysis was complete." Comment: possibly done.

Larsen 2012 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: the pharmacy labelled coded syringes with codes only known by them. Comment: possibly done.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No concerns.
Selective reporting (reporting bias)	Low risk	Quote: "This trial was registered at Clinicaltrials.gov as NCT00336908." Comment: the trial registration information was first posted on 14 June 2006. This was before the trial completion or analysis. All outcomes were reported.
Other bias	Unclear risk	Comment: the trial registration information on Clinicaltrials.gov mentioned the primary outcome as "To determine whether the sepsis and degree of the inflammation response is altered." However sepsis was mentioned as a secondary outcome in the study report. There was no difference in the sepsis in the 2 arms.

Lima 1988

Methods	Design: single-centre randomised controlled trial Setting: Departments of Child Health and Medical Biochemistry, University of Wales College of Medicine, Cardiff, UK I. Allocation concealment: not mentioned II. Blinding of intervention: not mentioned III. Blinding of outcome measurement(s): not mentioned IV. Complete follow-up: yes
Participants	Neonates receiving nil by mouth; total serum bilirubin < 100 µmol/L and tolerated intravenous nutrition consisting of dextrose and amino acids. The infants had a variety of illnesses such as respiratory problems requiring ventilation or major neonatal abdominal surgery (or both).
Interventions	51 infants enrolled. Group 1 (n = 26): MCT/LCT-based LE; Lipofundin (50% MCT/50% LCT; B Braun Medical) Group 2 (n = 25): S-LE; Intralipid (conventional 100% LCT emulsion; KabiVitrum) All neonates received similar parenteral infusates, apart from the LE. Amino acid solution (Vamin 9 (KabiVitrum)) was started on third day of life in an increasing dosage schedule up to 2.1 g/kg/day of amino acids. LE was administered on day 4 at initial doses of 0.5 g/kg/day for infants of < 1.5 kg birthweight and 1 g/kg/day for infants ≥ 1.5 kg birthweight. LE dosage increased daily by 0.5 g/kg up to a maximum of 3 g/kg/day. The LEs, placed in a syringe pump, were infused by the same route using a 'Y' connection tube near the infant, for 20 hours per day stopping from 5 a.m. to 9 a.m. Blood samples (1 mL) were collected at 9 a.m. before the daily LE infusion started. Samples were taken daily up to the 7th day of lipid administration and then weekly until the infants were discharged from the study.
Outcomes	Clinical and biochemical effects measured including weight gain, plasma triglycerides, cholesterol, ketones, free fatty acids and glucose.
Notes	

Lima 1988 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The infants were randomised into two lipid groups. The random procedure was the permuted blocks system to avoid imbalance in terms of number of infants between the groups." Comment: possibly done (by review author consensus).
Allocation concealment (selection bias)	Unclear risk	Comment: assessment of risk was not possible as allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The infants were randomised into two lipid groups." Comment: assessment of risk was not possible as blinding not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The infants were randomised into two lipid groups." Comment: assessment of risk was not possible as blinding not described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no major concerns.
Selective reporting (reporting bias)	Unclear risk	Comment: assessment of risk was not possible as protocol not available.
Other bias	Low risk	Comment: none identified.

Magnusson 1997

Methods	Design: double-blind, randomised controlled trial Setting: Department of Pediatric Surgery University Hospital Uppsala, Sweden I. Allocation concealment: could not determine II. Blinding of intervention: could not determine III. Blinding of outcome measurement(s): could not determine IV. Complete follow-up: yes
Participants	20 neonates of either sex, needing surgical treatment, aged ≤ 7 days and requiring TPN for ≥ 5 days. Exclusion criteria were: metabolic disease, renal disease, inflammatory disease, septic syndrome or a haematological disorder. Neonates undergoing surgery for various oesophago-gastrointestinal malformations were assigned the day after surgery.
Interventions	Group 1 (n = 10): BS-LE; PFE 4501 Group 2 (n = 10): S-LE; Intralipid The total amount of LE infused was 2 g/kg on the first day, which was increased at a daily rate of 1 g/kg until an infusion rate of 4 g/kg/day was reached

Magnusson 1997 (Continued)

Outcomes	Primary outcomes: changes in fatty acid composition in plasma and adipose tissue, plasma carnitine concentrations and tolerance during a short period of TPN. Heart rate, body temperature, body-weight and clinical symptoms were recorded daily. Haematological (haemoglobin, leukocytes and platelets) and biochemical (aspartate aminotransferase, ALT, sodium, potassium, creatinine, alkaline phosphatase, albumin and bilirubin) parameters were measured on day 0, just before the first infusion of TPN started, and after termination of the study.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "double-blind, randomised control trial." Comment: assessment of risk not possible. No details of randomisation.
Allocation concealment (selection bias)	Unclear risk	Comment: assessment of risk not possible as allocation concealment not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: assessment of risk not possible because authors did not describe how blinding was achieved. Most outcomes were objective, so impact may have been low.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: assessment of risk not possible because authors did not describe how blinding was achieved. Though most outcomes were objective. So the impact may be low.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no significant risk identified.
Selective reporting (reporting bias)	Unclear risk	Comment: assessment of risk was not possible as protocol not available.
Other bias	Low risk	Not identified.

Nehra 2014

Methods	Design: randomised, controlled, double-blind clinical trial Setting: Boston Children's Hospital, Boston, MA, USA Study enrolment: July 2007 to June 2009 I. Allocation concealment: yes II. Blinding of intervention: yes III. Blinding of outcome measurement(s): yes IV. Complete follow-up: no All analyses were performed on an intention-to-treat basis.
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Nehra 2014 (Continued)

Participants	<p>Inclusion criteria: neonates and infants (< 3 months of age) with baseline conjugated bilirubin < 1.0 mg/dL and a gastrointestinal disease requiring surgical intervention who were expected to be PN dependent for ≥ 21 days</p> <p>Exclusion criteria: baseline INR > 1.5 (> 2 if ≤ 1 week of age) or triglyceride level > 400 mg/dL and infants with a haemolytic disorder, liver disease, or shock requiring vasopressor support, extracorporeal membrane oxygenation, nitric oxide treatment or a combination of these. Infants who had undergone an intestinal lengthening procedure were not eligible.</p>
Interventions	<p>Group 1 (n = 9): pure F-LE; Omegaven</p> <p>Group 2 (n = 10): S-LE; Intralipid</p> <p>Infants received standard medical, surgical and nutrition support. Both LEs were provided at 1 g/kg/day throughout the study period. All patients remained on their assigned LE until weaned from PN unless crossed over to the other study arm. Infants with persistently elevated conjugated bilirubin (> 2 mg/dL for ≥ 2 continuous weeks) were considered treatment failures and were crossed over to the other study arm.</p>
Outcomes	<p>Primary: incidence of cholestasis, defined as a serum conjugated bilirubin > 2 mg/dL for ≥ 2 consecutive weeks</p> <p>Secondary: neurodevelopmental outcome assessed by BSID-III, a series of motor, cognitive, and language scales, at 6 and 24 months' corrected age</p>
Notes	<p>Study terminated because of low incidence of primary outcome.</p> <p>Trial registered at ClinicalTrials.gov (NCT 00512629)</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	<p>Quote: "Following informed consent, patients were randomly assigned by a computer-generated list of random numbers to the control (SIFE [soybean oil-based intravenous fat emulsion]) or experimental (FIFE [fish oil-based intravenous fat emulsion]) group in a 1:1 ratio."</p> <p>Comment: done.</p>
Allocation concealment (selection bias)	Low risk	<p>Quote: "Patients, parents, physicians, dieticians, and nurses were blinded to the treatment allocation for the duration of the study. Members of the department of pharmacy were aware of the randomisation and identically packaged the IFEs [intravenous fat emulsion]."</p> <p>Comment: probably done.</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "Patients, parents, physicians, dieticians, and nurses were blinded to the treatment allocation for the duration of the study. Members of the department of pharmacy were aware of the randomisation and identically packaged the IFEs."</p> <p>Comment: probably done.</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "Patients, parents, physicians, dieticians, and nurses were blinded to the treatment allocation for the duration of the study. Members of the department of pharmacy were aware of the randomisation and identically packaged the IFEs."</p> <p>Comment: probably done.</p>

Nehra 2014 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: clinical outcomes were reported for most infants. Secondary outcome: neurodevelopment outcome had significant loss to follow-up. By consensus the authors felt that the overall risk was unclear due to attrition. However, the absolute numbers were small and balanced (unlikely to have contributed to significant bias in 4-week outcomes).
Selective reporting (reporting bias)	Low risk	Quote: "This trial is registered at clinicaltrials.gov (NCT 00512629)." Comment: protocol was registered at the time of trial initiation and trial was reported in line with the published protocol.
Other bias	Unclear risk	Trial terminated early because of low incidence of primary outcome.

Pereira-da-Silva 2017

Methods	Design: single-centre, double-blind, randomised controlled trial Setting: NICU at Hospital Dona Estefania, Rua Jacinta Marto, Lisbon, Portugal Study enrolment: August 2011 to February 2014 I. Allocation concealment: yes II. Blinding of intervention: yes III. Blinding of outcome measurement(s): yes IV. Complete follow-up: yes
Participants	Inclusion criteria: infant with a gestational age ≥ 34 weeks who underwent surgery for a major anomaly of the digestive tract or of a congenital anomaly affecting the digestive tract (e.g. diaphragmatic hernia). Neonates were recruited within the first 48 postnatal hours, if PN (including lipids) had been initiated. Exclusion criteria: pre-existing hepatobiliary disease, such as biliary atresia, choledochal cyst, progressive intrahepatic familial cholestasis, infectious hepatitis, neonatal idiopathic hepatitis, biliary lithiasis, inborn errors of metabolism and abnormalities of markers of liver function or integrity within the first 72 postnatal hours
Interventions	49 infants completed study Group 1 (n = 22): MOFS-LE; SMOF lipid Group 2 (n = 27): MCT/SOY All participants were scheduled to receive an individualised PN within the first 24 postnatal hours, including amino acids, glucose, electrolyte and vitamins PN solution plus lipids (using SMOFlipid or MCT/SOY). As customised PN was not available during the weekends, infants admitted over weekends received a standard solution containing only glucose, calcium and amino acids. Parenteral lipid intake was reduced to 0.5 to 1.5 g/kg/day if hypertriglyceridaemia (> 250 mg/dL), hyperglycaemia (> 150 mg/dL), unconjugated bilirubin > 12 mg/dL, acute phase of sepsis or pulmonary hypertension occurred. If cholestasis was diagnosed, the parenteral intakes were limited to 2 to 2.5 g/kg/d of lipids, 2.0–2.5 g/kg/day of amino acids, and 12 mg/kg/minute of glucose. The same enteral feeding protocol was used in both groups. Minimal enteral feeding (10 mL/kg daily for 5 days) was initiated.
Outcomes	Primary outcome: incidence of cholestasis, defined initially as Cbil > 1 mg/dL (17.1 mmol/L). After the trial initiation, the primary outcome was further specified: Cbil > 1 mg/dL (17.1 mmol/L) if total bilirubin

Pereira-da-Silva 2017 (Continued)

bin was < 5 mg/dL (85.5 mmol/L) or a Cbil > 20% of the total bilirubin if this was > 5 mg/dL. Secondary outcome: initially set as the severity of cholestasis, evaluated by the magnitude of the conjugated bilirubinaemia and gamma-glutamyltranspeptidase > 225 IU/L. After the trial initiation, trialists also included as secondary outcome parameters total alkaline phosphatase > 608 IU/L; elevated ALT and AST, defined as > 55 IU/L in girls or > 60 IU/L in boys, as markers of PNALD. Analysis was planned to be made as per protocol; therefore, infants were excluded from analysis if PN was required for < 7 consecutive days, if the infant was transferred to another unit before completing 7 consecutive days of PN or if another liver-related disease was diagnosed.

Notes	PN exposure was similar in both groups: median (range) time on PN of 16 (7–72) days, 16 days in SMOF group vs 18 days in MCT/SOY group. Enrolment was prematurely interrupted because the MCT/SOY became unavailable, thus 49 infants (SMOF n = 22; MCT/SOY n = 27) completed the study.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Stratified randomisation by gestational age (term (37 weeks) vs. near-term (34 and < 37 weeks'))", Performed by pharmacy department. Comment: probably done (review author consensus).
Allocation concealment (selection bias)	Low risk	Quote: "performed by one pharmacist based at the hospital pharmacy to either 20% SMOF or 20% MCT/SOY." Comment: probably done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The masked IVLE [intravenous lipid emulsions] were packaged in plastic containers labelled with the patient name. Prescribing physicians and NICU staff were unaware of the patient group assignment. The pharmacist who randomised the participants was not aware of the liver status of the participants." Comment: by consensus the review authors assigned low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The masked IVLE were packaged in plastic containers" labelled with the patient name. Prescribing physicians and NICU staff were unaware of the patient group assignment. The pharmacist who randomised the participants was not aware of the liver status of the participants." Comment: by consensus the review authors assigned the study low risk for this bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not detected.
Selective reporting (reporting bias)	Unclear risk	Quote: "Trial registration number: ClinicalTrials.gov, NCT02633384." Comment: the trial registry date indicated 17 December 2015 for the first post on ClinicalTrials.gov. This was after the trial finished in February 2014. Comment: no decision was possible as prespecified protocol or study details were not available.
Other bias	Unclear risk	When 52 infants had been enrolled between August 2011 and December 2013 the study had to be stopped because MCT/SOY LE was no longer available at the hospital. Comment: unclear risk (and not high risk) as the trial was stopped due to the non-availability of the LE.

ALT: alanine aminotransferase; AST: aspartate transaminase; BS-LE: borage oil-soybean oil lipid emulsion; BSID-III: Bayley Scales of Infant and Toddler Development, 3rd edition; Cbil: conjugated bilirubin; F-LE: fish oil lipid emulsion; INR: international normalised ratio; LCT: long-chain triglyceride; LE: lipid emulsion; MCT: medium-chain triglyceride; medium-chain triglyceride-fish-soybean oil lipid emulsion; MOFS-LE: medium-chain triglyceride-olive-fish-soybean oil lipid emulsion; MS-LE: medium-chain triglyceride-soybean oil lipid emulsion; PDA: patent ductus arteriosus; PN: parenteral nutrition; PNAC: parenteral nutrition-associated cholestasis; PNALD: parenteral nutrition-associated liver disease; S-LE: soybean oil-based lipid emulsions; SD: standard deviation; TPN: total parenteral nutrition; TNF- α : tumour necrosis factor- α .

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Calkins 2014	People with intestinal failure-associated liver disease aged 2 weeks to 18 years. SO was replaced with fish oil (1 g/kg/day) in 10 participants who were receiving most of their calories from PN. Participants were compared with 20 historic controls receiving SO. SO for both groups was prescribed by the primary medical team at variable doses. Primary outcome: time to reversal of cholestasis.
Calkins 2017	Multicentre randomised controlled pilot study enrolled people with gastrointestinal disorders who were ≤ 5 days of age to a low dose (about 1 g/kg/day) or control dose of S-LE (about 3 g/kg/day). Primary outcome: cholestasis (conjugated bilirubin > 2 mg/dL) after the first 7 days of age.
Nehra 2013	Retrospective review of neonates admitted between 2007 and 2011 with a gastrointestinal condition necessitating ≥ 21 days of PN support. Neonates were divided into 2 groups based on the intravenous lipid emulsion dose: 1-g group (1 g/kg/day) and 2- to 3-g group (2 to 3 g/kg/day). Primary outcome: incidence of cholestasis.
Pichler 2014	Retrospective study included neonates/preterm infants and children with abnormal liver function tests, alanine transferase, alkaline phosphatase, gamma-glutamyltransferase 1.5 times upper limit of normal or total bilirubin 450 μ mol/L (or both) for > 2 weeks on treatment with PN containing pure soybean lipid emulsion (Intralipid 20%; Fresenius-Kabi), were started on/changed to SMOFlipid or Lipofundin. Results of biochemistry and clinical outcome were compared on commencing and discontinuing treatment according to the new LE used. Children aged 0–16 (median 0.6) years were included. 56 were given Lipofundin and 71 SMOFlipid. Addition of MCT to soybean LE was associated with improved liver function
Webb 2008	Double-blind, randomised study, conducted in critically ill neonates requiring PN in the first week of life. Infants were randomised to receive OS-LE (ClinOleic) or S-LE (Intralipid) for a minimum of 5 days. Plasma phospholipid fatty acids, F(2)-isoprostanes, liver function and clinical outcome assessed after 5 days of therapy. Interventions: 78 neonates (mean gestational age 37 weeks, range 26 to 41 weeks) received OS-LE (n = 39) or S-LE (n = 39). Reason for exclusion: significant number of preterm infants in the study.

OS-LE: olive-soybean oil lipid emulsion; PN: parenteral nutrition; S-LE: soybean oil lipid emulsion; SO: soybean oil.

DATA AND ANALYSES

Comparison 1. Fish oil LE versus non-fish oil LE in infants with surgical conditions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PNALD/cholestasis (conjugated bilirubin $\geq$ 2 mg/dL)	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.08, 15.28]
1.1 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.08, 15.28]
2 PNALD/cholestasis (any definition)	2	68	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.38, 3.76]
2.1 MOFS-LE vs MS-LE	1	49	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.35, 4.35]
2.2 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.08, 15.28]
3 Culture positive sepsis	2	51	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.47, 2.34]
3.1 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.39, 3.19]
3.2 MFS-LE vs S-LE	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.30, 3.32]
4 Any sepsis (clinical or culture positive (or both))	3	93	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.53, 2.02]
4.1 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.39, 3.19]
4.2 MFS-LE vs S-LE	1	32	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.41, 2.45]
4.3 MOFS-LE vs S-LE	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.95]
5 Necrotising enterocolitis (any stage)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.23, 4.40]
5.1 MOFS-LE (MCT-olive-fish-soybean oil) vs S-LE	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.23, 4.40]
6 Duration of ventilation (days)	1	32	Mean Difference (IV, Fixed, 95% CI)	2.10 [-0.95, 5.15]
6.1 MFS-LE vs S-LE	1	32	Mean Difference (IV, Fixed, 95% CI)	2.10 [-0.95, 5.15]
7 Length of stay (days)	1	32	Mean Difference (IV, Fixed, 95% CI)	5.10 [-9.59, 19.79]
7.1 MFS-LE vs S-LE	1	32	Mean Difference (IV, Fixed, 95% CI)	5.10 [-9.59, 19.79]
8 Hypertriglyceridaemia	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 MOFS-LE vs MS-LE	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.06, 1.01]
9 Conjugated bilirubin levels (μmol/L)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-33.52 [-50.60, -16.44]
9.2 Pure F-LE vs S-LE	1	14	Mean Difference (IV, Fixed, 95% CI)	0.0 [-11.30, 11.30]
10 Gamma-glutamyltransferase levels (IU/L)	2	38	Mean Difference (IV, Fixed, 95% CI)	24.85 [-63.21, 112.91]
10.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	63.68 [-44.12, 171.48]
10.2 Pure F-LE vs S-LE	1	14	Mean Difference (IV, Fixed, 95% CI)	-53.0 [-205.64, 99.64]
11 Alanine aminotransferase levels (IU/L)	2	38	Mean Difference (IV, Fixed, 95% CI)	-4.07 [-14.93, 6.79]
11.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-15.80, 10.20]
11.2 Pure F-LE vs S-LE	1	14	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-26.75, 12.75]
12 Alkaline phosphatase levels (IU/L)	2	38	Mean Difference (IV, Fixed, 95% CI)	-56.91 [-114.70, 0.87]
12.1 Pure F-LE vs S-LE	1	14	Mean Difference (IV, Fixed, 95% CI)	-96.0 [-236.52, 44.52]
12.2 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-48.96 [-112.35, 14.43]
13 Triglyceride levels (mmol/L)	2	38	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.44, 0.38]
13.1 MOFS-LE (MCT-olive-fish-soybean oil) vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.56, 0.92]
13.2 Pure F-LE vs S-LE	1	14	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.61, 0.37]
14 Death before discharge	3	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.1 MOFS-LE vs MS-LE	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Pure F-LE vs S-LE	1	19	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 MFS-LE vs S-LE	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 1 PNALD/cholestasis (conjugated bilirubin ≥ 2 mg/dL).

Analysis 1.2. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 2 PNALD/cholestasis (any definition).

Analysis 1.3. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 3 Culture positive sepsis.

Analysis 1.4. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 4 Any sepsis (clinical or culture positive (or both)).

Analysis 1.5. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 5 Necrotising enterocolitis (any stage).

Analysis 1.6. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 6 Duration of ventilation (days).

Analysis 1.7. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 7 Length of stay (days).

Analysis 1.8. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 8 Hypertriglyceridaemia.

Analysis 1.9. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 9 Conjugated bilirubin levels (μmol/L).

Analysis 1.10. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 10 Gamma-glutamyltransferase levels (IU/L).

Analysis 1.11. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 11 Alanine aminotransferase levels (IU/L).

Analysis 1.12. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 12 Alkaline phosphatase levels (IU/L).

Analysis 1.13. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 13 Triglyceride levels (mmol/L).

Analysis 1.14. Comparison 1 Fish oil LE versus non-fish oil LE in infants with surgical conditions, Outcome 14 Death before discharge.

Study or subgroup	Fish oil LE n/N	Non-fish oil LE n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 MOFS-LE vs MS-LE					
Pereira-da-Silva 2017	0/22	0/27			Not estimable
Subtotal (95% CI)	22	27			Not estimable
Total events: 0 (Fish oil LE), 0 (Non-fish oil LE)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.14.2 Pure F-LE vs S-LE					
Nehra 2014	0/9	0/10			Not estimable
Subtotal (95% CI)	9	10			Not estimable
Total events: 0 (Fish oil LE), 0 (Non-fish oil LE)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.14.3 MFS-LE vs S-LE					
Larsen 2012	0/16	0/16			Not estimable
Subtotal (95% CI)	16	16			Not estimable
Total events: 0 (Fish oil LE), 0 (Non-fish oil LE)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	47	53			Not estimable
Total events: 0 (Fish oil LE), 0 (Non-fish oil LE)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable

Comparison 2. Fish oil LE versus non-fish oil LE in infants with cholestasis

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Resolution of PNALD/cholestasis (conjugated bilirubin < 2 mg/dL)	1	16	Risk Ratio (M-H, Fixed, 95% CI)	5.6 [0.34, 93.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pure F-LE vs IL	1	16	Risk Ratio (M-H, Fixed, 95% CI)	5.6 [0.34, 93.35]
2 PNALD/cholestasis (any definition)	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.32, 0.91]
2.1 MOFS-LE vs S-LE	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.14, 1.10]
2.2 Pure F-LE vs IL	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.43, 1.13]
3 Time to resolution of PNALD (days)	1	16	Mean Difference (IV, Fixed, 95% CI)	-27.0 [-70.91, 16.91]
3.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	-27.0 [-70.91, 16.91]
4 Growth rate (g/week)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	45.0 [15.00, 75.00]
5 Head growth velocity (cm/week)	1	16	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.01, 0.33]
5.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.01, 0.33]
6 Any sepsis (clinical and/or culture positive)	2	40	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.50, 2.92]
6.1 MOFS-LE vs S-LE	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.52, 4.18]
6.2 Pure F-LE vs S-LE	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.14, 4.23]
7 Hypertriglyceridaemia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.09]
7.1 MOFS-LE vs S-LE	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.30, 2.09]
8 Hyperglycaemia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.52, 4.18]
8.1 MOFS-LE vs S-LE	1	24	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [0.52, 4.18]
9 Conjugated bilirubin levels (μmol/L)	1	24	Mean Difference (IV, Fixed, 95% CI)	-47.0 [-71.65, -22.35]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-47.0 [-71.65, -22.35]
10 Gamma-glutamyltransferase levels (IU/L)	1	24	Mean Difference (IV, Fixed, 95% CI)	115.00 [12.86, 217.14]
10.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	115.00 [12.86, 217.14]
11 Alanine aminotransferase (ALT) levels (IU/L)	1	24	Mean Difference (IV, Fixed, 95% CI)	-36.0 [-155.41, 83.41]
11.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-36.0 [-155.41, 83.41]
12 Alkaline phosphatase levels (IU/L)	1	24	Mean Difference (IV, Fixed, 95% CI)	-119.0 [-240.01, 2.01]
12.1 MOFS-LE vs S-LE	1	24	Mean Difference (IV, Fixed, 95% CI)	-119.0 [-240.01, 2.01]
13 Triglyceride levels (mmol/L)	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.85, 0.05]
13.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.85, 0.05]
14 Rate of change of ALT (IU/L/week)	1	16	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-14.79, -1.21]
14.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	-8.0 [-14.79, -1.21]
15 Rate of change of conjugated bilirubin (μmol/L/week)	1	16	Mean Difference (IV, Fixed, 95% CI)	-12.9 [-23.69, -2.11]
15.1 Pure F-LE vs S-LE	1	16	Mean Difference (IV, Fixed, 95% CI)	-12.9 [-23.69, -2.11]
16 Death before discharge	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.03, 1.87]
16.1 MOFS-LE vs S-LE	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.02, 8.69]
16.2 Pure F-LE vs S-LE	1	16	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.01, 2.88]

Analysis 2.1. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 1 Resolution of PNALD/cholestasis (conjugated bilirubin < 2 mg/dL).

Analysis 2.2. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 2 PNALD/cholestasis (any definition).

Analysis 2.3. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 3 Time to resolution of PNALD (days).

Analysis 2.4. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 4 Growth rate (g/week).

Analysis 2.5. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 5 Head growth velocity (cm/week).

Analysis 2.6. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 6 Any sepsis (clinical and/or culture positive).

Analysis 2.7. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 7 Hypertriglyceridaemia.

Analysis 2.8. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 8 Hyperglycaemia.

Analysis 2.9. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 9 Conjugated bilirubin levels (μmol/L).

Analysis 2.10. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 10 Gamma-glutamyltransferase levels (IU/L).

Analysis 2.11. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 11 Alanine aminotransferase (ALT) levels (IU/L).

Analysis 2.12. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 12 Alkaline phosphatase levels (IU/L).

Analysis 2.13. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 13 Triglyceride levels (mmol/L).

Analysis 2.14. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 14 Rate of change of ALT (IU/L/week).

Analysis 2.15. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 15 Rate of change of conjugated bilirubin (μmol/L/week).

Analysis 2.16. Comparison 2 Fish oil LE versus non-fish oil LE in infants with cholestasis, Outcome 16 Death before discharge.

ADDITIONAL TABLES

Table 1. Table of baseline characteristics of the included studies (Continued)

Study refer- ence	Intervention LE	Control LE								
	Lipid emulsion	n	Boys	Gestation (weeks)	Birth weight (mean ± SD; g)	Lipid emulsion	n	Boys	Gestation (weeks)	Birth weight (mean ± SD; g)
Angsten 2002	Vasolipid(50% MCT/50% LCT)	10	NR	38 (SD 1)	3341 (SD 428)	20% Intralipid	10	NR	36 (SD 1)	3073 (SD 588)
Ariyawangso 2014	SMOFlipid	21	13	< 37: n = 13 38–41: n = 8	2155 (SD 400.8)	20% Intralipid	21	11	< 37: n =14 38–41: n = 7	2136.2 (SD 407.4)
Diamond 2017	SMOFlipid	11	6	34.5 (range 32.4– 36.7)	2390 (range 1940– 2840)	20% Intralipid	13	7	35.2 (range 33.2– 37.1)	2550 (range 2130– 2980)
Lam 2014	10% Omegaven	9	6	29 (IQR 28–34)	1410 (IQR 770–2665)	10% Intralipid	7	4	29 (IQR 26–37)	1240 (IQR 870–2180)
Larsen 2012	50:40:10 mixture of MCT, soybean oil, and fish oil	16	10	40.3 (SD 2.4)	3.3 (SD 0.4)	20% Intralipid	16	NR	40.4 (SD 2.4)	3600
Lima 1988	50% MCT/50% LCT	26	NR	31 (SD 4.5)	1588 (SD 748)	20% Intralipid	25	NR	31.7 (SD 4.5)	1674 (SD 610)
Magnusson 1997	PFE 4501	10	NR	38 (SD 2)	2837 (SD 391)	20% Intralipid	10	NR	36 (SD 2)	2631 (SD 643)
Nehra 2013	Omegaven	9	5	36 (IQR 36.0–37.0)	2450 (IQR 2370– 2545)	20% Intralipid	10	4	34.5 (IQR 34–36)	2250 (IQR 1900– 2500)
Pereira-da-Silva 2017	SMOFlipid	22	13	38.5 (IQR 35.0–40.0)	2678 (IQR 2331– 3125)	MCT/SOY	27	13	37.0 (IQR 37.0–38.0)	2770 (IQR 2435– 2960)

IQR: interquartile range; LCT: long-chain triglyceride; MCT: medium-chain triglyceride; n: number of participants; PFE 4501: Paediatric fat emulsion 4501; SD: standard deviation; SOY: soybean.

APPENDICES

Appendix 1. Constituents of lipid emulsions used in the studies included in the review

Constituents	20% In- tralipid (Frese- nius-Kabi)	Lipoven- 2 (Fre- se- nius-Kabi)	2i- posyn III (Mos- pira)	PFE 4501 (Phar- macia Swe- den) ^a	Lipo- fundin-MCT/ LCT 20% (B Braun)	Struc- tolipid 20% (Frese- nius-Kabi)	Lipove- noes-MCT (Frese- nius - Kabi)	Cli- noleic 20% (Bax- ter)	Omegave- 6 (Fre- se- nius Kabi)	Lipoplus- 20 (B Braun)	20% SMOFlipid (Frese- nius-Kabi)
Oil source (%)											
Soybean oil	100	100	100	85	50	64	50	20	—	40	30
Coconut (MCT) oil	—	—	—	—	50	36	50	—	—	50	30
Olive oil	—	—	—	—	—	—	—	80	—	—	25
Fish oil	—	—	—	—	—	—	—	—	100	10	15
Borage oil	—	—	—	15	—	—	—	—	—	—	—
Composition of major fatty acids: % by weight of total fatty acids											
MCTs											
Caproic acid (6:0)	—	—	—	—	0.5	0.1	0.2	—	—	—	Trace
Caprylic acid (8:0)	—	—	—	—	29	26	30	—	—	30	17
Capric acid (10:0)	—	—	—	—	20	10	17	—	—	19	12
Lauric acid (12:0)	—	—	—	—	1	0.2	0.2	—	—	—	0.2
Long-chain triacylglycerols											
Myristic acid (14:0)	0.2	—	Trace	—	—	—	Trace	0.2	5	0.5	1
Palmitic acid (16:0)	10.8	12	11	11.2	7	7	7	12	12	6	9
Palmitoleic acid (16:1 ω-7)	—	—	Trace	—	—	—	0.2	1.5	9	0.6	2
Stearic acid (18:0)	4.2	5	4	4.1	2	3	3	2	4	2	3
Oleic acid (18:1 ω-9)	24	24	23	—	11	14	13	62	15	8	29

(Continued)

ω-6/ω-3 ratio	7:1	7:1	7:1	—	7:1	7:1	7:1	9:1	1:8	2.7:1	2.5:1
ω-6 long-chain triacylglycerols											
Linoleic acid (18:2 ω-6)	53	53	53	50.8	29	35	27	19	4.4	24	19
Arachidonic acid (20:4 ω-6)	0.1	—	—	—	0.2	—	—	0.5	2	—	0.5
ω-3 long-chain triacylglycerols											
α-linolenic acid (18:3 ω-3)	7	8	8.3	5.9	4	5	4	2	1.8	3	2
EPA (20:5 ω-3)	—	—	—	—	—	—	—	—	19	3	3
DHA (22:6 ω-3)	—	—	—	—	—	—	—	0.5	12	2	2
α-Tocopherol (mg/L)	38	—	—	—	85 (SD 20)	6.9	—	32	150–296	190	200
Other constituents											
Phytosterols (mg/L)*	439.1 (SD 5.7)	—	—	—	278.14 (SD 5.09)	—	—	274.4 (SD 2.6)	0	—	207
γ-Linolenic acid (18:3 ω-6)	—	—	—	3.2	—	—	—				
L-Carnitine	—	—	—	0.4	—	—	—				

Data collated from multiple sources including [Vanek 2012](#); [Vlaardingerbroek 2012](#); [Wanten 2007](#); [Xu 2012](#); and other references in the review.

DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; MCT: medium-chain triacylglycerol, NP: not provided; SD: standard deviation.

Lipoven is also known as Lipovenoes; Lipoplus is also known as Lipidem.

^aPharmacia group merged with Pfizer in 2002. No recent trials with PFE 4501 were identified and the current status of manufacturing could not be confirmed at the time of this review.

Appendix 2. Abbreviations for lipid emulsions

Pure soybean oil-based lipid emulsions (S-LE): lipid emulsions with 100% lipids derived solely from soybean oil:

- Intralipid;
- Ivelip;
- Liposyn III.

Fish oil-containing lipid emulsions: all fish oil-containing lipid emulsions (MOFS-LE, MFS-LE, and pure F-LE):

- MOFS-LE (MCT-olive-fish-soybean oil), e.g. SMOFlipid;
- MFS-LE (MCT-fish-soybean oil), e.g. Lipidem;
- pure F-LE (pure fish oil), e.g. Omegaven.

We also considered any other combination LE that contain fish oil if available at the time of the review.

Alternative lipid emulsions: all alternative lipid emulsions with partial or complete substitution of soybean oil from other sources (decreased linoleic acid content):

- OS-LE (olive-soybean oil), e.g. ClinOleic;
- MS-LE (MCT-soybean oil), e.g. Lipovenoes MCT;
- BS-LE (borage-soybean oil), e.g. PFE 4501;
- Structured lipids (structured MCT-soybean oil), e.g. Structolipid.

Specific lipid components have been denoted by the following letters: soybean by 'S'; MCT (from coconut oil) by 'M'; fish oil by 'F'; olive oil by 'O'; borage oil by 'B'. The abbreviations for the 'alternative lipid emulsion' end in the letter 'S' (if containing soybean oil) for consistency in nomenclature and to indicate the common theme of substitution of soybean oil by lipids from alternative sources (e.g. olive-soy is abbreviated as 'OS-LE'; MCT-soybean as 'MS-LE'; MCT-olive-fish-soybean as 'MOFS-LE'). Further, except the letter 'S' (which is always the last letter in the lipid emulsion abbreviations), the sequence of letters denoting the other lipid components are in the decreasing order of lipid percentage (as found in commonly available preparations), e.g. in MFS-LE (e.g. Lipidem), the percentage of MCT > percentage of fish oil; and in MOFS-LE (e.g. SMOFlipid) the percentage of MCT (30%) > percentage of olive oil (25%) > percentage of fish oil (15%).

Appendix 3. Comparisons of lipid emulsions

We will consider newer lipid emulsions with partial or complete substitution of soybean oil by lipids from other sources in the intervention group. We will also look at newer lipid emulsions compared to each other.

We will consider the following interventions/comparisons.

1. Fish oil-containing lipid emulsion versus all non-fish oil lipid emulsion

- MOFS-LE (MCT-olive-fish-soybean oil) versus S-LE
- MFS-LE (MCT-fish-soybean oil) versus S-LE
- Pure F-LE (pure fish oil) versus S-LE
- MOFS-LE, e.g. SMOFlipid versus OS-LE, e.g. ClinOleic
- MOFS-LE, e.g. SMOFlipid versus MS-LE, e.g. Lipovenoes MCT
- MOFS-LE, e.g. SMOFlipid versus BS-LE, e.g. PFE 4501
- MOFS-LE, e.g. SMOFlipid versus structured LE, e.g. Structolipid
- MFS-LE, e.g. Lipidem versus OS-LE, e.g. ClinOleic
- MFS-LE, e.g. Lipidem versus MS-LE, e.g. Lipovenoes MCT
- MFS-LE, e.g. Lipidem versus BS-LE, e.g. PFE 4501
- MFS-LE, e.g. Lipidem versus structured LE, e.g. Structolipid

- Pure F-LE, e.g. Omegaven versus BS-LE, e.g. PFE 4501
- Pure F-LE, e.g. Omegaven versus structured LE, e.g. Structolipid
- Pure F-LE, e.g. Omegaven versus MS-LE, e.g. Lipovenoes MCT
- Pure F-LE, e.g. Omegaven versus OS-LE, e.g. ClinOleic

We will also consider any other combination LE containing fish oil in this comparison if available at the time of the review.

2. Fish oil LE versus another fish oil-containing lipid emulsion

- MOFS-LE, e.g. SMOFlipid versus pure F-LE, e.g. Omegaven
- MFS-LE, e.g. Lipidem versus pure F-LE, e.g. Omegaven
- MOFS-LE, e.g. SMOFlipid versus MFS-LE, e.g. Lipidem

3. Alternative lipid emulsion versus pure soybean oil lipid emulsion (S-LE)

- OS-LE (olive-soybean oil) versus S-LE
- MS-LE (MCT-soybean oil) versus S-LE
- BS-LE (borage-soybean oil) versus S-LE
- Structured lipids (structured MCT-soybean oil) versus S-LE

4. Alternative lipid emulsion versus another alternative lipid emulsion

- OS-LE, e.g. ClinOleic versus MS-LE, e.g. Lipovenoes MCT
- OS-LE, e.g. ClinOleic versus BS-LE, e.g. PFE 4501
- OS-LE, e.g. ClinOleic versus structured LE, e.g. Structolipid
- MS-LE, e.g. Lipovenoes MCT versus BS-LE, e.g. PFE 4501
- MS-LE, e.g. Lipovenoes MCT versus structured LE, e.g. Structolipid
- BS-LE, e.g. PFE 4501 versus structured LE, e.g. Structolipid

Appendix 4. Search strategy

MEDLINE

Database: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Parenteral Nutrition/
2 infusions, intravenous/
3 Fat Emulsions, Intravenous/
4 (parenteral$ adj2 (fed or feed$ or nutrition$)).ti,ab.
5 (TPN or PPN or PN).mp.
6 (intravenous adj2 (infus$ or emulsion$)).ti,ab.
7 ("i.v." adj2 (infus$ or emulsion$)).ti,ab.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 exp Lipids/
10 (coconut$ or borage$ or fish$ or olive$ or soy$ or soybean$).mp.
11 ((alternative or conventional or multisource) adj LE).mp.
12 (alternative-LE or conventional-LE or multisource-LE).mp.
13 structured MCT$.mp.
14 (arachidon$ or BS-LE or clinoleic$ or DHA or docosahexaenoic acid$ or eicosapentaenoic acid$ or EPA or F-LE).mp.
15 (intralipid$ or ivelip$).mp.
16 (LCT$ or linolenic$ or linoleic$ or lipidem$ or lipoplus$ or liposyn$ or lipovenoes$ or lipofundin$).mp.
17 (MCT-fish or MCT-olive or MCT-soy or MFS-LE or MOFS$ or MOFSLE$ or MCT$ or MS-LE or MUFSS monounsaturated).mp.
18 (omega-6$ or omega-3$ or omegaven$ or OS-LE).mp.
19 (PFE 4501$ or PFE4501$ or polyunsaturated$ or PUFA$).mp.
20 (S-LE or SMOF$ or structolipid$ or triacylg$ or triglyc$).mp.
21 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 8 and 21
23 exp Infant, Newborn/
24 Premature Birth/
25 (neonat$ or neo nat$).ti,ab.

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26 (newborn\$ or new born\$ or newly born\$).ti,ab.
 27 (preterm or preterms or pre term or pre terms).ti,ab.
 28 (preemie\$ or premie or premies).ti,ab.
 29 (prematu\$ adj3 (birth\$ or born or deliver\$)).ti,ab.
 30 (low adj3 (birthweight\$ or birth weight\$)).ti,ab.
 31 (lbw or vlbw or elbw).ti,ab.
 32 infan\$.ti,ab.
 33 (baby or babies).ti,ab.
 34 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
 35 22 and 34
 36 randomised controlled trial.pt.
 37 controlled clinical trial.pt.
 38 randomized.ab.
 39 placebo.ab.
 40 drug therapy.fs.
 41 randomly.ab.
 42 trial.ab.
 43 groups.ab.
 44 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
 45 exp animals/ not humans.sh.
 46 44 not 45
 47 35 and 46

Appendix 5. Risk of bias tool

'Risk of bias' tool

1. Random 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. We assessed blinding 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. We assessed blinding 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 ($\geq$ 20% missing data) or
- unclear risk.

6. Selective reporting bias. Were 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. We assessed the methods as:

- low risk (where it was clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review were reported);
- high risk (where not all the study's prespecified outcomes were reported; one or more reported primary outcomes were not prespecified outcomes of interest and were reported incompletely and so could not 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 (e.g., 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 or
- unclear risk.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Appendix 6. Details of GRADE 'quality of evidence' decisions in the review and in the 'Summary of findings' tables

Assessment of risk of bias in a study (refer to the 'Risk of bias' tool in Appendix 5)

No risk of bias	No critical limitation in any criteria*
Moderate risk of bias	Critical limitation in 1 criteria or some limitations in > 1 criteria
High risk of bias	Critical limitation in > 1 criteria

* Criteria for assessing risk of bias in a study: lack of allocation concealment, lack of blinding, loss to follow-up or intention-to-treat analysis not performed, selective outcome reporting or other limitations.

Decision matrix to downgrade for 'quality of studies' in an outcome

Decision to downgrade	Risk of bias across studies for an outcome
Do not downgrade	Most information is from studies at low risk of bias
Downgrade 1 level	Most information is from studies at moderate risk of bias

(Continued)

Downgrade 2 levels

Most information is from studies at high risk of bias

The evidence was also downgraded for an outcome if there was significant contribution from a study or studies at high risk of bias in one or more key domains, that was sufficient to affect the interpretation of results.

If a study was terminated early, we downgraded the level of evidence in the review even if the study was assigned unclear risk of bias for early termination. This was done especially in outcomes with limited number of participants, or where the terminated study was the only study in the outcome or it was one of the two studies in the outcome with a significant contribution.

Decision matrix to downgrade for 'imprecision' in an outcome

Decision matrix for imprecision	CI do not cross null effect	CI cross null effect but not 0.75 or 1.25	CI cross null effect AND cross 0.75 or 1.25
OIS adequate	Do not downgrade	Do not downgrade	Downgrade 1 level
OIS inadequate	Downgrade 1 level	Downgrade 1 level	Downgrade 2 levels

Adequate optimal information size (OIS; empirical) for this review:

- for categorical variables: "300 or more total events in both groups;"
- for continuous variables: "minimum sample size of 400 participants" as a general approximation.

Evidence was downgraded by one level for those outcomes where there was only a single small study.

CI: confidence interval.

Decision matrix to downgrade for 'inconsistency' in an outcome

Decision matrix for inconsistency	Heterogeneity $I^2 > 40\%$ (40%-74%)	Unexplained high heterogeneity with $I^2 > 75\%$ and very low P value
Same direction of effect estimates in the studies	May not downgrade 1 level if most of the studies have similar point estimates and overlapping CI AND all point estimates are pointing in the same direction.	Downgrade 1 level
Different direction of effect estimates in the studies	Downgrade 1 level	Downgrade 2 levels

Heterogeneity could not be evaluated if there was a single study in an outcome.

Adapted from GRADE working group recommendations ([Schünemann 2013](#)).

CONTRIBUTIONS OF AUTHORS

For the original review ([Kapoor 2015](#)), all review authors were involved in conceiving and designing the protocol ([Kapoor 2018](#)).

RS, VK and MM performed the update of the protocol (2018) to address the requests of UK guideline developers of the [National Institute for Health Research](#) (NIHR).

VK and MM selected studies, extracted data and assessed risk of bias, relying upon RS as a third assessor when necessary. VK and MM prepared the manuscript, conferring and collaborating with RS.

DECLARATIONS OF INTEREST

VK none.

MM none.

RS none.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added some outcomes after the protocol stage as some of these outcomes made biological sense and have also been reported in studies other than the ones included in this review.

- PNALD/cholestasis using any definition
- Rate of change of alanine aminotransferase (IU/L/week).
- Rate of change of conjugated bilirubin ($\mu\text{mol/L/week}$).
- Any sepsis.

We added some outcomes for the Summary of findings tables after the protocol stage, i.e. hypertriglyceridaemia, any sepsis, conjugated bilirubin levels, ALP levels, and rate of change of conjugated bilirubin.

NOTES

This review and the companion review of "Lipid emulsions for parenterally fed preterm infants" will replace the published review titled "Alternative lipid emulsions versus pure soybean oil-based lipid emulsions for parenterally fed preterm infants" ([Kapoor 2015](#)).