Influence of different intravenous lipid emulsions on growth, development and laboratory and clinical outcomes in hospitalised paediatric patients: A systematic review

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Running title: Lipid emulsions in hospitalised paediatric patients

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Abstract

Background & aims: Fats in the form of lipid emulsions (LEs) are an integral part of intravenous nutrition. The fatty acid composition of different LEs varies. The exact composition of a LE may influence cell and tissue function and clinical outcome. Currently, it is not clear which LE might be best for paediatric patients. We conducted a systematic review of the effects of different intravenous LEs in hospitalised paediatric patients.

Methods: Randomised controlled trials published in a peer reviewed journal, written in the English language, and comparing two or more different intravenous LEs in hospitalised paediatric patients were included. Data on outcomes of relevance (growth, development, laboratory and clinical outcomes) were extracted, collated and interpreted.

Results: Thirty-one articles involving 1522 infants or children were included. Most outcomes were not affected by the nature of the LE used. LEs containing fish oil, a source of omega-3 fatty acids, improved outcome of retinopathy of prematurity, decreased liver cholestasis and increased blood omega-3 fatty acid levels. LEs containing olive oil increased blood oleic acid level and had a cholesterol lowering effect.

Conclusion: Blood fatty acids are influenced by the nature of the intravenous LE used in hospitalised paediatric patients. Most studies suggest limited differences in relevant laboratory or clinical outcomes or in growth in paediatric patients receiving different LEs, although several studies do find benefits from including fish oil or olive oil. There is a need for larger trials to fully evaluate the effects of the available LE types in hospitalised paediatric patients.

Keywords: Parenteral nutrition; lipid emulsion; fatty acid; triglyceride; fish oil

Abbreviations used: ALA, α-Linolenic acid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; DHA, docosahexaenoic acid; ELBW, extremely low birth weight; EPA, eicosapentaenoic acid; FA, fatty acid; GGT, gamma-glutamyl transpeptidase; HDL, high density lipoprotein; LA, linoleic acid; LCT, long chain triglyceride; LDL, low density lipoprotein; LE, lipid emulsion; MCT, medium chain triglyceride; MUFA, monounsaturated fatty acid; NEFA, non-esterified fatty acid; PN, parenteral nutrition; PUFA, polyunsaturated fatty acid; RCT, randomised controlled trial; ROP, retinopathy of prematurity; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TG, triglyceride; VLBW, very low birth weight.

1. Introduction

Nutrition plays a crucial role in supporting the growth, development and health of a child and is associated with optimal organ development and function, a strong immune system, a reduced incidence of childhood disease, and a lower risk of non-communicable diseases (such as cardiovascular disease and diabetes) in later life [1].

Nutritional support in hospitalised children is important in preventing nutrient deficits. Hospital-acquired malnutrition is associated with increased length of hospital stay, and greater risk of morbidity and mortality [2]. For the majority of infants and children, nutrition support can be delivered enterally. However, in the absence of enteral autonomy, nutrients are delivered parenterally (i.e. intravenously) to sustain growth and development. Situations where parenteral nutrition (PN) is required include premature neonates <1500 g or those with acquired or congenital gastrointestinal disorders such as gastroschisis or acute bowel obstruction, and complications arising from treatment for malignancy. For the majority of children, PN is required acutely, but in premature infants and others with congenital gastrointestinal disorders, PN may be used for the management of intestinal failure (defined as use of PN for greater than 28 days in children) which increases the risk of long term dependence [3].

Lipids, in the form of an emulsion, are needed in PN to provide non-carbohydrate energy, in a low volume and with a low osmolality, in addition to providing essential fatty acids [4,5]. Nitrogen balance may be improved through the addition of lipid emulsions (LEs) to PN [6]. LEs for use in PN are available in various compositions from several manufacturers (Table 1) and are made up of several parent oils with distinct fatty acid (FA) compositions and biological effects [4]. Different FAs have different physiological roles [7] and therefore the exact composition of a LE may influence laboratory biomarkers of cell and tissue function

and subsequent clinical outcome. Indeed, several studies suggest that different LEs impact clinical outcomes differently [4], although there is a paucity of evidence regarding overall superiority of one LE over another in terms of safety and/or efficacy.

Several systematic reviews investigating the safety and effects of various LEs in paediatric patients have been conducted, with mostly inconclusive results [8,9,10]. Typically these reviews have been limited to a small number of trials as they considered restricted patient populations and/or outcomes. Kotiya et al. [11], the most recent and largest systematic review in this field, reported benefits for both fish oil-based LEs (less incidence of cholestasis) and soybean oil-based LEs (reduction in duration of respiratory support) [11]. However, the patient population was restricted to preterm neonates or neonates with low birth weight, and not all outcomes of interest were considered. Hence, our aim was to conduct a systematic review to evaluate the effects different LEs have on a comprehensive range of growth, development and laboratory and clinical outcomes in hospitalised paediatric patients ranging from preterm infants to children aged up to 18 years.

2. Methodology

2.1 Literature search

This study was designed according to the guidelines of the 2009 preferred reporting items for systematic reviews and meta-analyses (PRISMA) [12]. Electronic databases and the reference lists of previous systematic reviews were used as the information sources to locate relevant studies for the review. The databases utilised were Medline (1946 to September 2015), Embase (1974 to 2015 September), Cochrane Central Register of Controlled Trials, CINAHL, AMED and PsyInfo. The searches were made from September to November 2015.

The search strategy was divided into four sections: population, PN, lipid, and clinical outcomes/laboratory parameters (Supplementary Table 1). To ensure that the search criteria captured all relevant articles, the chosen terms were discussed between two authors (R-RE and PCC) and compared to those found in past reviews. Articles were limited to *Full text* only.

2.2 Study selection

Studies which met the following criteria were included in the systematic review: full publication in a peer reviewed journal; randomised controlled trial (RCT) study design which compared two or more distinct intravenous LEs; written in the English language; participants were hospitalised paediatric patients; and the variables measured included one or more of growth, development, or laboratory or clinical outcome(s). Studies were excluded if they were qualitative studies, case reports, abstracts, review articles, commentaries, posters or conference proceedings; if they involved retrospective analysis or historic cohorts; if they made no comparison between two or more intravenous LEs; if they reported the effects of a change in LE type given to the same patient cohort or had no distinct intervention and control groups; or if other components of the PN (carbohydrates, amino acids etc.) were not kept to similar proportions.

Articles that did not meet the eligibility criteria were rejected. Articles that were unclear were retrieved in full for further inspection. To ensure a thorough literature search, the reference lists of previous systematic reviews were also checked manually. Figure 1 illustrates this multistep approach.

2.3 Publication bias

Publication bias was minimised by utilising multiple online databases in combination with manual reference searches. However, due to the language limitation to English, there is the potential for publication bias. Indeed, Egger (1997) demonstrated that "authors were more likely to publish RCTs in an English language journal if the results were statistically significant" [13].

2.4 Data extraction

Data were extracted in tabular form based on the eligibility criteria (Supplementary Table 2).

2.5 Quality assessment

To assess the biases within each study, the “The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials” was used [14].

3. Results

3.1 Search results

The electronic literature searches identified 2382 citations, and two extra studies were found from manual searches of the reference lists of past systematic reviews. Once duplicates were deleted, 1803 articles remained. Thirty-two articles met the inclusion criteria; however, two articles were based on the same study [15,16]. Therefore, 31 unique studies representing 1522 infants or children were included in the systematic review. Table 2 presents a descriptive summary of each included study.

With regard to assessment of bias, most of the studies had a “low chance of bias” for the majority of the categories, with a few having “uncertain risk of bias” for some categories. The other bias category was put to “uncertain risk of bias” as default unless “high risk of bias” was indicated in the article, because external biases (such as affiliations and funding) were not declared in the studies nor were ways of reducing external bias mentioned. Figure 2 illustrates the sources of bias within each study and Figure 3 depicts the percentage of studies that fell into a particular bias category.

3.2 Effect of parenteral lipid emulsions on body weight

Twenty studies (n=1012 infants and children) looked at the effects of different LEs on growth as measured by body weight gain or loss (Table 3) [17-36].

Five studies compared soybean oil with a blend of soybean oil and MCT [17-20,36]. The findings are inconsistent. Lehner et al. found that premature infants administered the blend lost an average 85 g of weight by day 8, while those in the soybean oil group gained ~12 g [17]. Lima et al. also suggest an advantage of soybean oil over a soybean oil/MCT blend in neonates [18]. They found a smaller weight loss in the soybean oil group (3.6 g/kg/day) compared to the blend group (4.9 g/kg/day) [18]. However, other studies comparing soybean

oil to other LEs (PFE 4501 or a soybean oil/MCT blend) showed no significant differences in weight gain between groups in either premature neonates or neonates up to 7 days old [19-21,36]. McClead et al. reported that neonates receiving soybean oil had a smaller weight gain (~14 g/day) than those receiving safflower oil (~18.4 g/day); those receiving a safflower oil/soybean oil blend had weight gain similar to soybean oil alone (~14 g/day) [22].

Four studies investigated weight gain in infants receiving an olive oil-based LE (80:20 olive oil/soybean oil blend) [23-25,36], but findings are again inconsistent. Three studies reported no significant difference between groups in either preterm neonates or older paediatric patients (aged 1-9 yr) with regard to weight gain [23,24,36], while Hartman et al. reported less weight gain in paediatric patients (aged between 1 and 18 yr) receiving an olive oil-based LE compared with a soybean oil-MCT blend [25].

Eleven studies investigated the effects of LEs including fish oil on body weight [26-36]. Lam et al. compared a pure fish oil-based LE with a soybean oil-based LE in infants and found that the increase in body weight was greater in the fish oil group (128 vs. 83 g/week) [26]. However, Nehra et al. [30] found no difference in weight gain between soybean oil and pure fish oil groups. D'Ascenzo et al. reported similar weight gain between a soybean oil/MCT/fish oil LE and soybean oil/MCT in extremely low birth weight (ELBW) infants, but the data were not shown [27]. Among the 11 studies of fish oil containing LEs, 7 compared soybean oil/MCT/olive oil/fish oil with other LEs [28,29,32-36]. These studies have shown inconsistent results with regard to body weight. D'Ascenzo et al. showed a greater postnatal weight loss (14.3 vs. 11.1%) and longer time from birth to the day of the regained birth weight (13.4 vs. 10.5 days) in ELBW infants with soybean oil/MCT/olive oil/fish oil compared to soybean oil [28]. In contrast, Vlaardingerbroek et al. reported increases in weight gain z scores with soybean oil/MCT/olive oil/fish oil from birth to time of discharge in very low birth weight (VLBW) infants whilst soybean oil resulted in a decrease in z scores [29]. The other 5 studies found no differences in weight gain between soybean oil and soybean oil/MCT/olive

oil/fish oil groups [32-36]. Overall 7 studies showed no difference in weight gain between groups receiving fish oil or fish oil containing blends and comparator LEs [30-36]. From the inconsistencies in these results, it must be concluded that there is not enough evidence to support the superiority of one particular LE over another with regard to maintenance or gain in body weight in paediatric patients.

3.3 Effect of parenteral lipid emulsions on change in head circumference and body length

Nine studies (n=373 infants and children) investigated the effects of different LEs on growth measured as head circumference (eight studies [23,24,26,27,29,30,32,33]) or body length/height (seven studies [23,24,27,30,32-34]) (Table 3). Seven of 8 studies reported no difference in head circumference in infants receiving different LEs [23,24,26,27,30,32,33]. However, although Vlaardingerbroek et al. reported no significant difference in head circumference between VLBW infants receiving soybean oil/MCT/olive oil/fish oil or soybean oil, the z scores for infants in the soybean oil/MCT/olive oil/fish oil group increased significantly more from birth to discharge [29]. Six of 7 studies reported no difference in body length/height in infants or children receiving different LEs [23,24,27,30,32,33]. However, Rayyan et al. observed an increase in head circumference in premature infants receiving soybean oil/MCT/olive oil/fish oil, whilst there was no change in the comparator group receiving soybean oil [34].Overall, strong evidence for superiority of one LE over another for supporting increase in head circumference or body length is lacking.

3.4 Effect of parenteral lipid emulsions on neurodevelopment

Long chain polyunsaturated fatty acids, especially the omega-3 FA docosahexaenoic acid (DHA), are important in brain growth and development and neuronal function [37-39]. Despite this, only one study (n=19 infants) has investigated the effect of LEs on neurodevelopment (Table 4) [30]. Nehra et al. compared pure fish oil and soybean oil in neonates; neuro-development was assessed using the “Bayley Scores of Infant

Development III" and the "Parent Report of Children's Abilities–Revised". There were no differences between groups in cognitive, language, or motor outcomes [30].

3.5 Effect of parenteral lipid emulsions on morbidity and mortality

Twenty-three studies (n=1208 infants and children) measured or reported the effects different LEs had on morbidity or mortality (Table 5) [15-19,21,23-26,29-36,40-45]. Most of these studies observed few, if any, differences between groups (Table 5). Köksal et al. reported that a total of 29 premature infants (45.3% of the study population) developed bronchopulmonary dysplasia [44]. Nine of these were in the olive oil group (31% of infants in that group) and 20 were in the soybean oil group (69% of infants in that group) [44]. The duration of mechanical ventilation was shorter in the olive oil group than in the soybean oil group (12.4 days vs. 34.6 days) [44]. Other conditions, such as respiratory distress syndrome, retinopathy of prematurity (ROP), necrotising enterocolitis, intraventricular haemorrhage and neonatal sepsis were not different between the groups [44]. Pawlik et al. diagnosed cholestasis six-times more frequently in premature infants receiving a soybean oil/olive oil LE than in those receiving a soybean oil/olive oil + fish oil (65:35) blend (n=20 vs. 3) [31]. Also in this study, 10 of the 19 infants who developed ROP in the fish oil-supplemented soybean oil/olive oil group experienced spontaneous regression [31]. However, in the soybean oil/olive oil group, 22 of the 26 infants who developed ROP required treatment. Laser therapy for ROP was used twice as often in the soybean oil/olive oil group than in the fish oil-supplemented soybean oil/olive oil group (n=22 vs 9) [31]. Beken et al. noted a higher number of VLBW neonates receiving soybean oil suffered with hypoglycaemic events compared with neonates receiving soybean oil/MCT/olive oil/fish oil [45]. Moreover, only two patients (5.0%) in the soybean oil/MCT/olive oil/fish oil group were diagnosed with ROP while 13 (32.5%) were diagnosed in the soybean oil group [45]. Overall, the evidence suggests that there may be benefits from fish oil containing LEs towards the development of ROP and PN-associated cholestasis in premature infants.

3.6 Effect of parenteral lipid emulsions on fatty acid levels

Higher levels of eicosapentaenoic acid EPA and DHA in plasma or red blood cells (RBCs) are found in paediatric patients receiving pure fish oil or fish oil containing blends compared to those receiving other LEs (Table 6) [27,28,30,32,34,35]. Several of these studies also report lower levels of arachidonic acid with fish oil administration (e.g. [28,32]). Olive oil-based LEs were shown to increase plasma or RBC oleic acid [23-25,42,43].

3.7 Effect of parenteral lipid emulsions on plasma triglyceride levels

Many studies report a rise in plasma triglycerides when LEs are infused, which is explained by the fact that the LE is almost entirely composed of triglyceride. However, an important question is whether different LEs affect plasma triglycerides differently. Twenty studies (n=946 preterm neonates, infants and children) reported the effects of different LEs on plasma triglycerides (Table 7) [17-21,24-30,34,35,40,42-46].

Rubin et al. noted higher plasma triglycerides in premature infants receiving soybean/MCT compared to those receiving soybean oil alone or PFE 4501 [20]. However, many studies found no significant differences between soybean oil and other LEs [17-19,21,46,47]. Several of the studies that compared an olive oil-based LE (80:20 olive oil/soybean oil) with other LEs also showed no difference in plasma triglycerides [24,40,42,44], although one such study reported higher triglycerides when olive oil rather than MCTs was used in combination with soybean oil [25].

Eight studies investigated the effects of fish oil or fish oil containing blends on plasma triglycerides [26-30,34,35,45]. Two studies showed no difference between a pure fish oi LE and comparator LEs for plasma triglyceride levels [26,30]. D'Ascenzo et al. reported a decrease over time in plasma triglycerides in ELBW infants receiving either soybean oil/MCT/fish oil or soybean oil/MCT but with no difference between groups [27]. In a later study, D'Ascenzo et al. reported higher plasma triglycerides in ELBW infants receiving

soybean oil/MCT/olive oil/fish oil than in those receiving soybean oil [28]. Other studies reported no difference in triglycerides in infants receiving soybean oil/MCT/olive oil/fish oil compared with other LEs [29,34,35,45]. Thus, the evidence is inconclusive as to whether there is a superior LE with regard to plasma triglyceride levels.

3.8 Effect of parenteral lipid emulsions on plasma cholesterol levels

Eighteen studies reported the effects of different LEs on plasma cholesterol (Table 7) [17-21,24-30,34,35,40,42,44,46]. Twelve of these studies reported no difference between LEs [17,21,26,27,29,30,34,35,40,42,44,46].

Rubin et al. reported a larger rise in plasma cholesterol in infants receiving soybean oil/MCT than those receiving soybean oil [19]. Conversely, Lima et al. reported a greater rise in plasma cholesterol in infants receiving soybean oil compared to those receiving soybean/MCT [18]. A later study by Rubin et al. supports Lima et al. and also suggests a greater rise in plasma cholesterol in those receiving soybean oil compared to the other LEs [20].

Goulet et al. showed lower plasma cholesterol in paediatric patients (aged 1-9 yr) after using an olive oil-based LE compared with soybean oil [24], an effect also reported by Hartman et al. in paediatric patients (aged between 1 and 18 yr) [25]. However, other studies using olive oil-based LEs showed no difference in plasma cholesterol compared with other LEs [40,42,44].

Five studies found no difference in plasma cholesterol in neonates receiving fish oil containing LEs and those receiving soybean oil [26,29,30,34,35] or soybean oil/MCT [27]. D'Ascenzo et al. reported no difference in plasma cholesterol between infants receiving soybean oil/MCT/fish oil or soybean oil [27]. In a later study, D'Ascenzo et al. reported a higher cholesterol level in the soybean oil/ MCT/olive oil/fish oil group infused at a rate of 3.5

g/kg/day compared to other groups (soybean oil/MCT/olive oil/fish oil at 2.5 g/kg/day and soybean oil at either 2.5 or 3.5 g/kg/day) [28].

Thus, there is evidence that olive oil-based LE may have a beneficial cholesterol lowering effect.

3.9 Effect of parenteral lipid emulsions on liver enzymes and bilirubin

Seventeen studies (n=922 infants and children) compared different LEs with regard to the liver enzymes alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transpeptidase (GGT) or total bilirubin (Table 8) [20,23-25,26,28-30,32-36,40,42,44,45]. If a LE was adversely affecting the liver, the concentrations of these parameters would be expected to increase.

Twelve out of 13 studies that reported ALT found no difference between LEs (Table 8). Seven out of 9 studies that reported AST found no difference between LEs (Table 8). Eleven out of 12 studies that reported GGT found no difference between LEs (Table 8). Thirteen out of 14 studies that reported total bilirubin found no difference between LEs (Table 8). Thus, any impact of LEs of different composition on liver enzymes and bilirubin seems to be minor. Rubin et al. found that the levels of AST decreased in infants receiving soybean oil or soybean oil/MCT compared to PFE 4501 [20]. Lam et al. reported a greater rate of increase in ALT in infants receiving soybean oil compared to those receiving a fish oil based LE [26]. However, Nehra et al. observed no significant differences in ALT, AST or GGT between those receiving fish oil based LE or soybean oil [30]. Tomsits et al. reported an increase in GGT over time with soybean oil compared with a decrease in the soybean oil/MCT/olive oil/fish oil group [35]. Vlaardingerbroek et al. observed a higher AST in infants receiving soybean oil/MCT/olive oil/fish oil on day 7 compared to those receiving soybean oil, although values were still within the normal range for preterm infants [29]. Rayyan et al. observed higher total bilirubin in the soybean oil/MCT/olive oil/fish oil compared with soybean oil [34].

In conclusion, the evidence does not point towards a particular LE being superior in terms of effect on liver enzymes or total bilirubin.

3.10 Effect of parenteral lipid emulsions on markers of oxidative stress

Four studies investigated the effects of different LEs on F2-isoprostane levels as a marker of oxidative stress (Table 9) [23,32,43,50],. F2-isoprostanes are formed by non-enzymatic oxidative modification of arachidonic acid [48,49]. Thiobarbituric acid reactive substances (TBARS) are another index of lipid peroxidation and oxidative stress, and are related to malondialdehyde, a product formed from oxidative breakdown of polyunsaturated fatty acids. Total antioxidant capacity (TAC) is a measure of the potential to withstand oxidative stress.

Three studies observed a decrease in plasma F2-isoprostanes over time in infants receiving either olive oil-based or soybean oil LEs, with no difference between the LEs [23,43,50]. Hartman et al. reported no difference in plasma TBARS between infants receiving olive oil-based LE or soybean oil/MCT [25]. Köksal et al. observed a decrease in plasma TAC over time in premature infants receiving olive oil-based LE or soybean oil LE with no difference between groups [44].

Deshpande et al. reported lower plasma F2-isoprostanes after soybean oil/MCT/olive oil/fish oil than after olive oil-based LE in preterm infants [32]. Plasma malondialdehyde, an indicator of lipid peroxidation related to TBARS, decreased over time with both soybean oil/MCT/olive oil/fish oil and the soybean oil with no difference between groups [35].

Thus, the available studies do not suggest a superior LE with respect to beneficial effects on oxidative stress.

3.11 Effect of parenteral lipid emulsions on “routine” blood parameters

Thirteen studies reported information on blood parameters, with the vast majority finding no differences between LEs (Table 10) [21,24-30,32-34,45]. However, Tomsits et al. noted a higher haemoglobin, haematocrit and RBC count in premature infants receiving soybean oil compared with those receiving soybean oil/MCT/olive oil/fish oil [35].

3.12 Effect of parenteral lipid emulsions on inflammatory markers

Five studies have reported no difference in C-reactive protein (CRP) concentration between infants receiving fish oil blends and comparator LEs (Table 10) [15,16,27,32-35]. However, Larsen et al. observed that the mean plasma concentrations of TNF-α, IL-1β and IL-6 in newborn infants were lower with soybean oil/MCT/fish oil than with soybean oil [15,16]. Gawecka et al. compared the effects of soybean oil and olive oil-based LEs over 14 days in premature infants on the cytokines produced by peripheral blood mononuclear cells in culture. After 14 days of treatment, TNF-α and IL-10 production were not different between groups. However, IL-6 synthesis was significantly higher in the soybean oil group compared to baseline, but there was no difference between the two groups (Table 10) [41]. Overall, evidence relating use of different LEs to inflammation is not consistent, but studies suggest little impact.

4. Discussion

This systematic review is the first to fully explore the effects that various LEs have on a comprehensive range of growth, development, laboratory and clinical outcomes in paediatric patients ranging from preterm infants to children < 18 years of age. The majority of studies did not find significant differences between the use of different LEs and growth, liver enzymes, plasma triglycerides, oxidative stress, blood parameters and inflammatory markers, which is consistent with the findings of four previous systematic reviews investigating the safety and possible beneficial effects of different LEs in preterm infants (n=3) and children (n=1) [8-11].

In terms of the effects of LEs on morbidity outcomes, one study showed a potential benefit of fish oil-containing blends on the incidence of cholestasis [31]. This supports the findings of the systematic review of Kotiya et al., who found significantly lowered incidence of cholestasis with fish oil blends vs soybean oil or soybean oil/olive oil blends in premature and low birth weight neonates [11]. This may in part be due to the lower concentrations of phytosterols present in fish oil blends compared with predominantly soybean oil based LEs, high levels of which have been linked with PN-associated cholestasis [51].

Two studies also showed a potential benefit of fish oil-containing blends on lowering the risk of ROP [31,45]. ROP was not an investigated outcome in three of the earlier systematic reviews [9-11] whilst the review of Vlaardingerbroek et al. [8] predates both relevant studies [31,45]. Fish oil contains significant amounts of both EPA and DHA and the abundance of DHA in fish oil is likely to be responsible for the beneficial effect on ROP. DHA comprises 20% of the infant retina [45]. DHA increases the formation of cytoprotective and anti-inflammatory metabolites, especially neuroprotectin D1, resolvin D1, and resolvin E1 [52]. By enhancing vessel regrowth, these mediators reduce neovascularisation after a vascular injury or loss

[53]. An alternative mechanism is that the DHA metabolite 4-hydroxy-DHA (4-HDHA) inhibits endothelial cell proliferation and sprouting angiogenesis [54]. It is important to note that the incidence of ROP was high in those studies that reported a benefit of fish oil.

Although not reviewed in detail here, several studies observed significantly higher levels of plasma or RBC EPA and DHA in infants receiving the fish oil or fish oil blend LEs compared to other LE groups [27,28,30,32,34,35]. EPA and DHA possess a number of biological activities that might be useful in paediatric patients requiring PN. For example, EPA and DHA are anti-inflammatory and regulate metabolism and organ function [7,52]. Several studies also reported significantly increased levels of plasma or RBC oleic acid in infants receiving olive oil-based LEs relative to other LEs [23-25,42,43]. Unlike PUFAs, oleic acid renders LDL cholesterol more resistant to oxidation [55]. This is important as it is the oxidised LDLs that have pro-atherogenic effects and contribute to major cardiovascular diseases such as atherosclerosis [56]. Furthermore, two meta-analyses noted that replacement of saturated FAs with oleic acid is associated with a cholesterol-lowering and LDL cholesterol-lowering effect [57,58]. This is consistent with the findings of Goulet et al. and Hartman et al. of significantly lowered cholesterol levels in the olive oil LE group compared to the soybean oil-based LE groups [24,25].

Interestingly, the use of soybean oil LE did not result in the expected overproduction of proinflammatory mediators [41,59,60]. However, fish oil-based LEs and blends that included fish oil did have the expected anti-inflammatory effect, lowering production of inflammatory cytokines, although only one study investigated this specific outcome [15,16]: Larsen et al. observed lower concentrations of TNF-α, IL-1β and IL-6 in infants receiving a fish oil blend [15,16]. Arachidonic acid is synthesised from the essential n-6 fatty acid linoleic acid and is commonly considered to suppress cell-mediated immunity and promote inflammation [7,52]. EPA and DHA, which are found in high concentrations in fish oil-containing LEs, are involved in mechanisms that antagonise the actions of arachidonic acid [7,52]. Therefore the

441 elevations in EPA and DHA that accompany administration of fish oil containing LEs are
442 linked directly to cell function changes that in turn are linked to clinical outcome [7,52].
443 Furthermore, EPA and DHA give rise to mediators that resolve inflammation [61,62].
444
445 The overall inconclusive nature of the results from measurement of a number of growth,
446 clinical and laboratory parameters is attributed to variable findings of the different studies. In
447 part this is due to variations in sample size among the studies included suggesting that there
448 was either no effect from the LEs, the study duration was too short to observe an effect, or
449 the studies were too small. Furthermore, one study that investigated the effects of LEs on
450 neurodevelopment reported no differences between LE groups. Overall, some studies
451 agreed on significant findings but the majority showed no differences between LE groups. It
452 is important to acknowledge that the current systematic review includes data from a very
453 heterogeneous group of paediatric patients of greatly varying ages and clinical situation.
454 Furthermore the literature included was published over the period from 1988 to 2015; over
455 this time patient treatment and nutrition support protocols have changed greatly.
456
457 With reference to future research, the findings of this systematic review emphasise the need
458 for larger studies to fully evaluate the effects of the available LEs in paediatric patients. Such
459 studies should be large RCTs that compare groups of patients on specific LEs. Fish oil/fish
460 oil blends and olive oil-based LEs are in need of further research to explore the potential for
461 clinical benefits that have been identified in this systematic review. Furthermore, additional
462 research into neurodevelopment is needed to gain a true perspective of the effects different
463 LEs.

5. Conclusion

PN is a necessary form of nutrition support for preterm infants and children who are unable to meet their nutritional needs through the oral or enteral routes. Emulsified lipids are an essential component of PN providing energy sources, essential fatty acids, bioactive fatty acids and lipid soluble vitamins. A variety of LEs are available for use in PN. The compositional differences of FAs in LEs offer the potential for a range of physiological effects impacting on growth and development, immune function, inflammatory response to illness, metabolism and subsequent clinical outcomes. In this systematic review RCTs investigating effects of LEs in paediatric patients were evaluated according to a range of outcomes including growth, neurodevelopment, clinical outcomes and clinically relevant laboratory outcomes. Findings from most of these studies suggest that there are limited differences in relevant laboratory or clinical outcomes and in growth of paediatric patients receiving different LEs as part of PN. Small sample size and differences in study design may be a factor in the failure to identify differences. However, several studies do find benefits from including fish oil or olive oil within LEs, for example in development of ROP and PN-associated cholestasis and in lowering plasma cholesterol, respectively, but overall there is inconsistency in results arising from RCTs. There is a need for larger trials to fully evaluate the effects of the available LEs (particularly fish oil- and olive oil-based LEs) in paediatric patients, with a focus on pre-term infants as they represent the largest single users of PN amongst the paediatric population.

Conflict of Interest

PCC has advised Fresenius-Kabi, B. Braun and Baxter Healthcare on the science of IVLEs. R-RE, JKI and LVM have no conflicts to report.

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684 **Table 1**.Lipid types, commercial names and compositions[1]

Lipid type	Commercial name	Composition
Soybean oil	Intralipid	Soybean oil
	Lipovenoes	Soybean oil
	Lipofundin N	Soybean oil
	Ivelip	Soybean oil
Soybean oil blend	Liposyn II	50:50 Safflower oil/Soybean oil
	Paediatric Fat Emulsion 4501	85:15 Soybean oil/Borage oil
	Lipofundin MCT/LCT or Médialipide	50:50 Soybean oil/MCT
Olive oil	Clinoleic	80:20 Olive oil/Soybean oil
Fish oil	Omegaven	Fish oil
Fish oil blend	SMOFLipid	30:30:25:15 Soybean oil/MCT/Olive oil/Fish oil
	Lipoplus (Lipidem in the UK)	40:50:10 Soybean oil/MCT/Fish oil
Safflower oil	Liposyn	Safflower oil

*MCT: Medium chain triglycerides; [1] Data taken from publications using those lipids and from manufacturers' websites.

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Table 2
Studies included in the systematic review and a summary of the outcomes reported

Author and year	Location of study	Patient group (weight and age)	Sample size at random-isation stage	Lipid emulsions compared	Lipid emulsions dose(s) used	Outcomes reported			
						Growth	Neuro-development	Clinical outcomes	Laboratory outcomes
Beken et al., 2013 [45]	Turkey	VLBW infants (<1500 g, <32 wk)	80	Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	Initially 0.5 g/kg/d in infants <1000 g or 1.0 g/kg/day in infants >1000 g, increasing by 0.5 to 1 g/kg daily up to a maximum of 3.0 g/kg/d			✓	✓
D'Ascenzo et al., 2011 [27]	Italy	ELBW infants (500 to 1249 g)	47	Soybean oil/ MCT/Fish oil vs Soybean oil/ MCT	0.5, 1.0, 1.5, 2.0, and 2.5 g/kg/d from postnatal day 0 to day 5, respectively. The highest dose was infused until day 7, when parenteral nutrition tapering was begun, until day 18, when it was stopped.	✓		✓	✓
D'Ascenzo et al., 2014 [28]	Italy	ELBW infants (500 to 1249 g)	80	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	Both at 2.5 and 3.5 g/kg/d	✓		✓	✓
Demirel et al., 2011 [40]	Turkey	VLBW infants (<1500 g, <32 wk)	40	Soybean oil vs Olive oil/ Soybean oil	Started on the second day of life at 1 g/kg/d and increased by 1 g/kg daily up to 3 g/kg/d			✓	✓
Deshpande et al., 2014 [32]	Australia	Preterm infants (<30 wk)	34	Soybean oil/MCT/ Olive oil/Fish oil vs Olive oil/ Soybean oil	7 day trial with an ascending dose every day: 1, 2, 3 and then 4 g/kg/d (for 4 d)	✓		✓	✓
Deshpande et al., 2009 [23]	Australia	Preterm infants (23 to 28 wk)	50	Soybean oil vs Olive oil/ Soybean oil	0.5, 1, 2 and 3 g/kg/d for 20 hours on 4 consecutive days	✓		✓	✓

Gawecka et al., 2008 [41]	Poland	Premature infants (<1500 g, <32 wk)	44	Soybean vs Olive oil/ Soybean oil	Started within 72 hr of life at 1 g/kg/d and was increasing to a maximum of dose of 3-3.5 g/kg/d			✓	✓
Göbel et al., 2003 [42]	Germany	Premature infants (28 to <37 wk)	45	Soybean oil vs Olive oil/ Soybean oil	0.5, 1.0, and 2.0 g/kg/d on the first 3 consecutive study days, respectively and then 2.0 g/kg/d for 4 d			✓	✓
Goulet et al., 1999 [24]	France	Children (1-9 yr, with short-bowel syndrome, intractable diarrhea or chronic intestinal pseudo-obstruction)	18	Soybean oil vs Olive oil/ Soybean oil	0.25 g/kg/d from between 18:00 and 20:00 to between 06:00 and 08:00 3–5 d/wk.	✓		✓	✓
Hartman et al., 2009 [25]	Italy	Children (<18 yr, who had undergone bone marrow transplantation)	28	Soybean oil/ MCT vs Olive oil/Soybean oil	Dose not given	✓		✓	✓
Köksal et al., 2011 [44]	Turkey	Premature infants (<34 wk)	64	Soybean oil vs Olive oil/ Soybean oil	1, 2 and 3 g/kg/d over the first 3 consecutive d, respectively, and then at 3 g/kg/d continuously for the next 4 d.			✓	✓
Lam et al., 2014 [26]	Hong Kong	Neonates with PN associated cholestasis	16	Soybean oil vs Fish oil	Starting dose of 0.5 g/kg/d gradually advanced to 1.5 at 0.5 g/kg/d increments every 2 days.	✓		✓	✓
Larsen et al., 2012 and 2015 [15,16]	Canada	Newborn infants scheduled to have open heart surgery with cardiopulmonary bypass for congenital heart disease)	32	Soybean oil vs MCT/Soybean oil/ Fish oil	Initially at 0.5 g/kg/d and gradually increased to a maximum of 3.5 g/kg/d			✓	✓

Lehner et al., 2006 [17]	Hungary	Premature infants (<3000 g, 25-37 wk)	15	Soybean oil vs Soybean oil/ MCT	Dose not given	✓		✓	✓
Liet et al., 1999 [63]	France	Preterm infants	14	Soybean oil vs Soybean oil/ MCT	1 g/kg/d starting on d 2, increasing at a rate of 1 g/kg/d to reach 3 g/kg/d by d 3.				✓
Lima et al., 1988 [18]	UK	Neonates (age not given, a variety of illnesses)	51	Soybean oil vs Soybean oil/ MCT	0.5 g/kg/d for infants <1.5 kg birthweight and 1 g/kg/d for ≥1.5 kg birthweight. Increased by 0.5 g/kg/d up to a maximum of 3 g/kg/day	✓		✓	✓
Magnusson et al., 1997 [21]	Sweden	Neonates (up to and including 7 d, with various esophageal gastrointestinal malformations)	20	Soybean oil vs PFE 4501	2 g/kg/d increased to 4 g/kg/d with daily increments of 1 g/kg	✓		✓	✓
McClead et al., 1991 [22]	USA	Infants (age not given, with a variety of diagnoses)	26	Soybean oil vs Safflower oil vs Safflower oil/ Soybean oil	Approx. 1.5 g/kg/d	✓		✓	✓
Nehra et al.,2014 [30]	USA	Neonates and infants (<3 months, with gastrointestinal disease and requiring surgical intervention)	19	Soybean oil vs Fish oil	1 g/kg/d	✓	✓	✓	✓
Pawlik et al., 2014 [31]	Poland	Premature infants (1250 g, <32 wk)	130	Olive oil/Soybean oil vs Olive oil/ Soybean oil + Fish oil (65:35)	1 g/kg/d initially; increased by 0.5 g/kg every 24 hr for infants < 1000 g and by 1 g/kg every 24 h for infants > 1000 g up to a maximum of 3.5 g/kg/d.	✓		✓	✓
Rayyan et al., 2012 [34]	Belgium	Premature infants (<34 wk)	53	Soybean oil vs Soybean	1.0 g/kg/d on d 1,2 and 3; 2 g/kg/d on d 4; 3 g/kg/d on d	✓		✓	✓

				oil/ MCT/ Olive oil/ Fish oil	5; 3.5 g/kg/d from d 6 to d 14				
Rhodes et al., 1991 [64]	USA	Preterm infants (<1500 g)	22	Soybean oil vs Safflower oil/ Soybean oil	1.5 g/kg/d for 7 days				✓
Roggero et al., 2010 [50]	Italy	Preterm infants (>700 g, 28–33 wk)	36	Soybean Oil vs Olive oil/ Soybean Oil vs Soybean Oil/ MCT	Started at 0.75 g/kg/d then increased to 1.0, 1.5, 2 and 2.5 g/kg/d for the subsequent 4 days respectively. Then infused at 3.0 g/kg/d				✓
Rubin et al., 1991 [19]	Israel	Premature infants (<34 wk)	30	Soybean Oil Vs Soybean Oil/ MCT	1.0 g/kg/d on d 1; 2 g/kg/d on d 2; 3 g/kg/d on d 3 until end of study period	✓		✓	✓
Rubin et al., 1995 [20]	Israel	Premature infants (<35 wk)	49	Soybean Oil vs Soybean Oil/ MCT vs PFE 4501	0.5 g/kg/d on d 1; 1.5 g/kg/d on d 2; 2.5 g/kg/d on d 3 until end of study period	✓		✓	✓
Savini et al., 2013 [36]	Italy	Preterm infants (500–1249 g)	150	Soybean oil vs Soybean oil/ MCT vs Soybean oil/ MCT/Fish oil vs Olive oil/ Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	1, 1.5, 2, 2.5, and 3 g/kg/d from postnatal days 0 to 5, respectively, and then kept constant from d 5 to 7, when PN tapering was begun, until day 21, when it was stopped.	✓		✓	✓
Skouroliakou et al., 2010 [33]	Greece	Premature infants (<1500 g, <32 wk)	38	Soybean oil vs Soybean oil/ MCT/ Olive oil/ Fish oil	PN started on second day of life at the latest, with the maximum dose being 3 g/kg/d and anticipated duration of 47 d	✓		✓	✓
Smuts et al., 1999 [46]	South Africa	VLBW infants (<1500 g, <32 wk)	40	10% Soybean oil	The fat emulsions were infused through either a				✓

				(Lipovenous) vs 10% Soybean oil (Intralipid) vs 20% Soybean oil (Lipovenous) vs 20% Soybean oil (Intralipid)	central or a peripheral vein over a 14-16 hour period each day, starting at a rate of ~1 g/kg/day and increasing by 0.5 -1.0 g/kg each successive day to a maximum of 3 g/kg/day on day 9.				
Tomsits et al., 2010 [35]	Hungary	Premature infants (1000–2500 g, 34 wk)	60	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	Initially at 0.5 g/kg/d on d 1 increasing by 0.5 g/kg each day up to a maximum of 2 g/kg/day from d 4 to 14.	✓		✓	✓
Vlaardingerbroek et al., 2014 [29]	Netherlands	VLBW infants (<1500 g)	98	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	2 g/kg/d within 6 hr after birth and increased at d 2 to 3 g/kg/d	✓		✓	✓
Webb et al., 2008 [43]	Australia	Neonates (≥25 wk of gestation to <7 days of age)	93	Soybean oil vs Olive oil/ Soybean oil	Initially 0.5 g/kg/d increasing to 1.0, 2.0 and 3.0 g/kg/d each day for the first 4 d and then remaining 3.0 g/kg/d until study end or lipid emulsion was discontinued.			✓	✓

Table 3
Summary of key features and findings of studies investigating the effect of different lipid emulsions on infant growth.

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on body weight (measured as at least one of body weight, body weight change, time to regain birth weight)	Effect on head circumference	Effect on body length or height
D'Ascenzo et al., 2011 [27]	ELBW infants (500 to 1249 g)	Soybean/MCT vs Soybean oil/MCT/ Fish oil	No significant difference between the groups	No significant difference between the groups	No significant difference between the groups
D'Ascenzo et al., 2014 [28]	ELBW infants (500 to 1249 g)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	Greater weight loss with fish oil blend (14.3 ± 5.8% vs. 11.1 ± 5.7%; p=0.015). Longer time from birth to the day of regained birth weight in fish oil blend group (13.4 ± 5.6 d vs. 10.5 ± 5.1 d; p=0.021). Weight gain from regained birth weight to 36 weeks post-menstrual age was not different between groups.	Not reported	Not reported
Deshpande et al., 2014 [32]	Preterm infants(<30 wk)	Olive oil/Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups
Deshpande et al., 2009 [23]	Preterm infants (23 to <28 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	No significant difference between groups	No significant difference between groups
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	No significant difference between groups	No significant difference between groups
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/MCT vs Olive oil/Soybean oil	Greater weight gain in the soybean oil/MCT	Not reported	Not reported

			group: at the end of follow-up (d 14) the body weight z-score was -0.43 ± 0.4 compared to -0.86 ± 0.4 at the start of PN while the olive oil/ soybean oil group weight z-score was -0.26 ± 0.3 compared to -0.35 ± 0.3 at the start of PN; p= 0.03.		
Lam et al., 2014 [26]	Infants (age not given)	Soybean oil vs Fish oil	Greater body weight gain with fish oil:128 vs. 83 g/week; p=0.02	No significant difference between groups	Not reported
Lehner et al., 2006 [17]	Premature infants (<3000 g, 25-37 wk)	Soybean oil vs Soybean oil/MCT	Greater weight gain with soybean oil: 11.7 g by d 8 vs. -85 g by d 8 (p value not given). But no difference between groups in z score for weight: mean(SD) 0.79 (1.20) vs. 0.78 (0.70)	Not reported	Not reported
Lima et al., 1988 [18]	Neonates (age not given)	Soybean oil vs Soybean oil/MCT	Weight gain from infant birthweight to weight on last day of PN feeding: -4.9 g vs. -3.6 g (p value not given)	Not reported	Not reported
Magnusson et al., 1997 [21]	Neonates (up to and including 7 d)	Soybean oil vs PFE 4501	No significant difference between groups	Not reported	Not reported
McClead et al., 1991 [22]	Infants (age not given)	Soybean oil vs Safflower oil vs Safflower/Soybean oil	Greater weight gain with safflower oil compared to safflower/soybean oil or soybean oil: 18.4 ± 8.5 g/day 14 ± 9.4 g/day 13.8 ± 3.7 g/day, respectively (p value not given)	Not reported	Not reported

Nehra et al., 2014 [30]	Neonates and infants (< 3 months)	Soybean oil vs Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups
Pawlik et al., 2014 [31]	Premature infants (1250 g, <32 wk)	Soybean oil/Olive oil vs Soybean oil/ Olive oil + Fish oil	No significant difference between groups	Not reported	Not reported
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No significant difference between groups	Not reported	Greater increase with fish oil blend: baseline = 38.9 ± 3.8 cm vs. 39.1 ± 3.2 cm; last observation = 40.7 ± 3.8 cm vs. 40.7 ± 3.3 cm, p<0.01
Rubin et al., 1991 [19]	Premature infants (<34 wk)	Soybean Oil vs Soybean Oil/MCT	No significant difference between groups	Not reported	Not reported
Rubin et al., 1995 [20]	Premature infants (<35 wk)	Soybean Oil vs Soybean Oil/MCT vs PFE 4501	No significant difference between groups	Not reported	Not reported
Savini et al., 2013 [36]	Preterm infants (500–1249 g)	Soybean oil vs Soybean oil/MCT vs Soybean oil/MCT/Fish oil vs Olive oil/Soybean oil Vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	Not reported	Not reported
Skouroliakou et al., 2010 [33]	Premature infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk,)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	Not reported	Not reported
Vlaardingerbroek et al., 2014 [29]	VLBW infants (birth weight <1500 g)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	Higher in fish blend group at time of discharge causing significant increase in z scores, whilst soybean	No significant difference between groups, but z scores for the infants in the fish oil blend group increased	Not reported

			oil group z scores decreased. (p=0.012)	more from birth to discharge compared with those in the control group (P=0.008).	

Table 4

Summary of key features and findings of a study investigating the effect of different lipid emulsions on infant neurodevelopment.

Author and year	Patient group (age)	Lipid emulsions compared	Effect on neuro-development outcome
Nehra et al., 2014 [30]	Neonates and infants (<3 months age)	Soybean oil vs Fish oil	No differences between groups in cognitive, language, or motor outcomes or in verbal or non-verbal cognition

Table 5

Summary of key features and findings of studies investigating the effect of different lipid emulsions on clinical outcomes.

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on clinical outcomes
Beken et al., 2013 [45]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No difference between groups for the incidence of respiratory distress syndrome, duration of oxygen therapy, duration of mechanical ventilation, number of RBC transfusions or number of hyperglycemic events. Number of hypoglycemic events was higher in soybean oil/MCT/olive oil/fish oil group ($p = 0.039$). Two patients (5.0%) in fish oil blend group and 13 patients (32.5%) in the soybean oil/MCT group were diagnosed with retinopathy of prematurity ($p = 0.004$). In each group only one patient needed laser photocoagulation.
Demirel et al., 2011 [40]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Olive oil/Soybean oil	No significant differences between groups for complications of prematurity such as respiratory distress syndrome, necrotising enterocolitis, bronchopulmonary dysplasia and retinopathy of prematurity. Fewer patients in the olive oil/soybean oil group received antibiotic therapy because of clinical and laboratory sepsis but the difference was not statistically significant (20% vs 35% $p=0.48$).
Deshpande et al., 2014 [32]	Preterm infants (<30 wk)	Soybean oil/MCT/ Olive oil/Fish oil vs Olive oil/Soybean oil	No significant difference between groups in incidence of positive blood cultures
Deshpande et al., 2009 [23]	Preterm infants (23 to <28 wk)	Soybean oil vs Olive oil/Soybean oil	One participant in the olive oil/soybean oil group died on day 2 (grade IV intraventricular haemorrhage). Two patients died before completion of the study following withdrawal of care due to respiratory failure.
Gawecka et al., 2008 [41]	Premature infants (<1500 g, <32 wk)	Soybean oil vs Olive oil/Soybean oil	No significant differences between groups in duration of mechanical ventilation or oxygen dependence or incidence of bronchopulmonary dysplasia, necrotising enterocolitis, retinopathy of prematurity, nosocomial infection or mortality

Göbel et al., 2003 [42]	Premature infants (28 to <37 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups in clinical events, including bradycardia, gastroesophageal reflux, hyperbilirubinemia, and apnea.
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive oil/Soybean oil	Adverse events (e.g. catheter-related sepsis) occurred between days 30 and 60 in 1 patient in the olive oil/soybean oil group and in 2 patients in the soybean oil group, but were resolved completely.
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/MCT vs Olive oil/Soybean oil	No significant differences between groups with regard to the success of engraftment, or post-transplantation time to engraftment.
Köksal et al., 2011 [44]	Premature infants (<34 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups for respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage or neonatal sepsis. Fewer infants in the olive oil/soybean oil group developed bronchopulmonary dysplasia: 31% vs 69% ($p < 0.05$). Duration of mechanical ventilation was shorter in olive oil/soybean oil group: 12.4±4.7 d v. 34.6±5.3 d ($p < 0.05$)
Lam et al., 2014 [26]	Neonates (age not given)	Soybean oil vs Fish oil	No difference between groups in the medium age of resolution of cholestasis. However, 3 of the 9 infants in the fish oil group recovered from parenteral nutrition-associated cholestasis while receiving PN, whilst none in the soybean oil group did. There were 2 deaths in the soybean oil group. Both died from hepatic and multi-organ failure secondary to septicaemia. All infants in the fish oil group survived and were discharged from hospital
Larsen et al., 2012, 2015 [15,16]	Infants (age not given)	Soybean oil vs Soybean oil/MCT/ Fish oil	No difference between groups for ventilator settings, ventilator days, "Pediatric Risk of Mortality" and "Risk-Adjusted Congenital Heart Surgery". The difference in length of stay between the groups (41.7±5.3 d vs. 46.8±5.3 d) was not statistically significant.
Lehner et al., 2006 [17]	Premature infants (<3000 g, 25-37 wk)	Soybean oil vs Soybean oil/MCT	No dropout was related to any adverse effects of the LEs.
Lima et al., 1988 [18]	Neonates (age not given)	Soybean oil vs Soybean oil/MCT	No significant difference between groups in mortality
Magnusson et al., 1997 [21]	Neonates (up to and including 7 d)	Soybean oil vs PFE 4501	Two patients in the PFE 4501 group with physiological icterus needed treatment with UV radiation.

Nehra et al., 2014 [30]	Neonates and infants (<3 mo)	Soybean oil vs Fish oil	No significant difference between groups in number of patients with ≥1 positive blood culture.
Pawlik et al., 2014 [31]	Premature infants (1250 g, <32 wk)	Olive oil/Soybean oil vs Olive oil/ Soybean oil + Fish oil	No significant differences between groups for use of oxygen or need for mechanical ventilation. Retinopathy of prematurity (ROP) (stages 1–3) occurred in 10 patients in the olive oil/soybean oil + fish oil group and all spontaneously regressed, while in the olive oil/soybean oil group 26 infants developed ROP and 22 of these required further treatment. Laser therapy for ROP was used twice as often in the olive oil/soybean oil group (22 vs 9; p value not given). Cholestasis diagnosed 6 times more frequently in the olive oil/soybean oil group (20 vs 3; risk ratio 0.18, p value not given)
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	75 adverse effects in 29 patients were observed (11 in the soybean oil/MCT/olive oil/fish oil group and 18 in the soybean oil group) during the treatment period. Six infants experienced serious side effects: two of these resulted in death – the cause was pneumothorax in the soybean oil/MCT/olive oil/fish oil group and Enterobacter sepsis in the soybean oil group. Almost all of the serious side effects were assessed as “not related to study drug,” apart from the Enterobacter sepsis in the soybean oil group, which was rated as “possibly” related to the study drug.
Rubin et al., 1991 [19]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT	No significant side effects were attributable to either LE.
Savini et al., 2013 [36]	Preterm infants (500–1249 g)	Soybean oil vs Soybean oil/MCT vs Soybean/MCT/ oil/Fish oil vs Olive oil/Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant differences between groups in bronchopulmonary dysplasia, patent ductus arteriosus, necrotising enterocolitis, and sepsis.
Skouroliakou et al., 2010 [33]	Premature infants (<1500g, <32 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No significant difference between groups in the type, dose and duration of antibiotic therapy, the days of ventilation support, maximum inspired oxygen fraction or the days of

			phototherapy. None of the patients developed sepsis.
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant differences between groups in number of adverse events, including infections and infestations, and respiratory, thoracic and mediastinal disorders.
Vlaardingerbroek et al., 2014 [29]	VLBW infants (birth weight <1500 g)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant differences between groups in total length of hospital stay or mortality.
Webb et al., 2008 [43]	Neonates (≥25 wk of gestation <7 d of age)	Soybean oil vs Olive oil/Soybean oil	No difference between groups in mortality

Table 6

Summary of key features and findings of studies investigating the effect of different lipid emulsions on fatty acid profiles

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on fatty acid profile
D'Ascenzo et al., 2011 [27]	ELBW infants (500 to 1249 g)	Soybean oil/MCT vs Soybean oil/MCT/Fish oil	On d 7, plasma DHA was significantly higher in the fish oil group ($p = 0.02$). Plasma EPA increased significantly in the fish oil group throughout the study period in comparison with those receiving soybean oil/MCT ($p < 0.001$). On d 7 and on d 14, RBC DHA and EPA were significantly higher in the fish oil group.
D'Ascenzo et al., 2014 [28]	ELBW infants (500 to 1249 g)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	On d 7 and d 14 plasma oleic, EPA and DHA were higher in soybean oil/MCT/olive oil/fish oil group (both doses) than in the soybean oil group, while linoleic and arachidonic acids were lower.
Deshpande et al., 2014 [32]	Preterm infants (<30 wk)	Olive oil/Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	Some RBC fatty acid changes over time. On d 8 RBC EPA was lower than at baseline in the olive oil/soybean oil group but was higher than baseline in the soybean oil/MCT/olive oil/fish oil group. On d 8, arachidonic acid and DHA were reduced as compared with baseline and similar in both groups.
Deshpande et al., 2009 [23]	Preterm infants (23 to <28 wk)	Soybean oil vs Olive oil/Soybean oil	Some RBC fatty acid changes over time. RBC oleic acid increased in the olive oil/soybean oil group. On d 6 RBC linoleic acid was higher in the soybean oil group than in the olive oil/soybean oil group.
Göbel et al., 2003 [42]	Premature infants (28 to <37 wk)	Soybean oil vs Olive oil/Soybean oil	A significant increase was observed in plasma phospholipid oleic acid in the olive oil/soybean oil group whilst there was a decrease in the soybean oil group, but the soybean group had a larger increase in linoleic acid. A significantly increased level of α-linolenic acid was observed in the soybean oil group than the olive oil/soybean oil group. In both groups, there was a significant drop in arachidonic acid, DHA and total n-6- and n-3-metabolites and total saturated fatty acids. EPA was unchanged in both groups.
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive	At d 60, there were significant differences between groups in

		oil/Soybean oil	fatty acids in plasma phospholipids. Oleic acid was higher in the olive oil/soybean oil group while linoleic acid and EPA were lower. RBC linoleic acid was higher in the soybean oil group than in the olive oil/soybean oil group
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/MCT vs Olive oil/Soybean oil	On d 14 serum oleic, linoleic and arachidonic acids were higher in the olive oil/soybean oil group; no significant difference in serum EPA and DHA between groups.
Larsen et al., 2012, 2015 [15,16]	Infants (age not given)	Soybean oil vs Soybean oil/MCT/Fish oil	On d1, d7 and d10 plasma phospholipid omega-3 fatty acids were higher in the soybean oil/MCT/ fish oil group than in the soybean oil group
Lehner et al., 2006 [17]	Premature infants(<3000 g, 25-37 wk)	Soybean oil vs Soybean oil/MCT	Some plasma fatty acid changes over time. On d 8, 8:0 and 10:0 were higher in the soybean oil/MCT group than in the soybean oil group. Plasma TG DHA was significantly higher in the soybean oil/MCT group on d 8.
Magnusson et al., 1997 [21]	Neonates	Soybean oil vs PFE 4501	Fatty acid composition changes over time. Plasma lipid γ-linolenic acid increased in the PFE 4501 group and plasma TG and phospholipid DHA decreased.
McClead et al., 1991 [22]	Infants (age not given)	Soybean oil vs Safflower oil vs Safflower oil/Soybean oil	There were some differences in plasma α-linolenic acid (safflower oil/soybean oil>safflower oil $p<0.05$; soybean oil>safflower oil $p<0.01$; safflower oil/soybean oil>soybean oil week 1 only, $p<0.05$). A significant increase in plasma EPA was seen in the safflower oil/soybean oil group compared to the safflower oil group, but there was no difference relative to the soybean oil group. There were also some differences in plasma DHA (safflower oil/soybean oil>safflower oil $p<0.05$; soybean oil >safflower oil $p<0.01$; soybean oil>safflower oil/soybean oil week 1 only $p<0.005$). Plasma linoleic acid increased in all three groups (safflower oil>safflower oil /soybean oil or soybean oil $p<0.05$). Plasma arachidonic acid remained stable but there were some differences (safflower oil/soybean oil>soybean oil $p<0.05$). Plasma oleic and eicosatrienoic acids decreased in all three groups. The decrease in oleic acid was less in soybean oil group compared to the other two groups ($p<0.01$).

Nehra et al., 2014 [30]	Neonates and infants (<3 mo)	Soybean oil vs Fish oil	Time dependent increase in plasma EPA, docosapentaenoic acid, DHA and total omega-3 fatty acids in the fish oil group. Time dependent increase in linoleic acid, γ-linolenic acid, dihomo-γ-linolenic acid and total omega-6 fatty acids in the soybean oil group.
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	Plasma and RBC linoleic and α-linolenic acids were higher in the soybean oil group than in the soybean oil/MCT/olive oil/fish oil group Plasma EPA and DHA were higher in the soybean oil/MCT/olive oil/fish oil group than in the soybean oil group.
Rhodes et al., 1991 [64]	Preterm infants (<1500 g)	Soybean oil vs Safflower oil/Soybean oil	Fatty acid composition changes over time but no significant differences between groups.
Smuts et al., 1999 [46]	VLBW infants (<1500 g, <32 wk)	10% Soybean oil (Lipovenous/LV) vs 10% Soybean oil (Intralipid /IL) vs 20% Soybean oil (Lipovenous/LV) vs 20% Soybean oil (Intralipid/IL)	Plasma phosphatidylcholine (PC) LA and ALA increased, but DGLA, arachidonic acid (AA) and EPA decreased during 10% TPN ($p < 0.05$). Plasma PC DHA decreased relative to other groups in the 10% LV group. RBC DGLA and AA decreased in the 10% LV group ($p<0.05$). Plasma MUFA were reduced in 20% IL compared to the LV group, mainly due to the reduction in oleic acid ($p=0.025$). DHA was more reduced in the 20% LV compared to the 20% IL, while the ratio of n-6 to n-3 fatty acids was increased more in the LV group ($p=0.037$). ALA was higher in the LV group, particularly in the 20% group ($p=0.017$).
Tomsits et al., 2010 [35]	Premature infants (1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	On d14 RBC EPA was higher in the soybean oil/MCT/olive oil/fish oil group than in the soybean oil group. The time dependent decrease in RBC DHA was partly prevented in the soybean oil/MCT/olive oil/fish oil group. On d14 RBC linoleic and α-linolenic acids were higher in the soybean oil group than in the soybean oil/MCT/olive oil/fish oil group
Vlaardingerbroek et al., 2014 [29]	VLBW infants (<1500 g)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	Significant increase in phospholipid n-3 to n-6 fatty acid ratio in the fish oil group (on days 6 and 14 in the study) compared to the soybean oil group.

Webb et al., 2008 [43]	Neonates (≥25 wk of gestation <7 days of age)	Soybean oil vs Olive oil/Soybean oil	Time dependent changes in fatty acid composition. On d 5 plasma phospholipid oleic acid was higher in the olive oil/soybean oil group than in the soybean oil group while linoleic acid was lower.

Table 7

Summary of key features and findings of studies investigating the effect of different lipid emulsions on blood triglycerides or cholesterol.

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on blood triglycerides (measured in plasma or serum)	Effect on blood cholesterol (measured in plasma or serum)
Beken et al., 2013 [45]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	No significant difference between groups	Not reported
D'Ascenzo et al., 2011 [27]	ELBW infants (500 to 1249 g)	Soybean oil/ MCT vs Soybean oil/ MCT/Fish oil	No significant difference between groups	No significant difference between groups
D'Ascenzo et al., 2014 [28]	ELBW infants (500 to 1249 g)	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	Significant increase in the 3.5 g/kg/d SMOF group vs. 2.5 g/kg/d SMOF group; 3.5 g/kg/d soybean oil group and 2.5 g/kg/d soybean oil group (231 ± 59 mg/dl vs. 132 ± 50 mg/dl vs. 166 ± 47 mg/dl vs. 119 ± 87 mg/dl; p=0.01).	Significant increase in the 3.5 g/kg/d SMOF group vs. 2.5 g/kg/d SMOF group; 3.5 g/kg/d soybean oil group and 2.5 g/kg/d soybean oil group (~70 mg/dl vs. ~50 mg/dl vs. ~50 mg/dl vs. ~50 mg/dl; p<0.05).
Demirel et al., 2011 [40]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	No significant difference between groups
Göbel et al., 2003 [42]	Premature infants (28 to <37 wk)	Soybean oil vs Olive oil/ Soybean oil	No significant difference between groups	No significant difference between groups
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive oil/ Soybean oil	No significant difference between groups	Lower with olive oil/soybean oil (3.67 ± 0.48 vs 3.91 ± 0.31 (mmol/L); p=0.047)
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/ MCT vs Olive oil/Soybean oil	Lower with soybean oil/MCT (113.1 ± 14.3 vs 157.1 ± 18.5 (mg/dL); p=0.067)	Higher wiyh soybean oil/MCT (144.4 ± 7.2 vs. 137.5 ± 8.1 (mg/dL); p=0.017)
Köksal et al., 2011	Premature infants	Soybean oil vs	No significant difference between	No significant difference between

[44]	(<34 wk)	Olive oil/Soybean oil	groups	groups
Lam et al., 2014 [26]	Neonates (age not given)	Soybean oil vs Fish oil	No significant difference between groups	No significant difference between groups
Lehner et al., 2006 [17]	Premature infants (<3000 g, 25-37 weeks)	Soybean oil vs Soybean oil/MCT	No significant difference between groups	No significant difference between groups
Lima et al., 1988 [18]	Neonates (age not given)	Soybean oil vs Soybean oil/MCT	No significant difference between groups	Lower with soybean oil/MCT (2.5 ± 0.08 vs. 4.12 ± 0.14 (mmol/l) p<0.001)
Magnusson et al., 1997 [21]	Neonates (up to and including 7 d)	Soybean oil vs PFE 4501	A slight increase was seen in the soybean oil group and a significant decrease in PFE 4501 group	No significant difference between groups
Nehra et al., 2014 [30]	Neonates and infants (<3 mo)	Soybean oil vs Fish oil	No significant difference between groups	No significant difference between groups
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No significant difference between groups	No significant difference between groups
Rubin et al., 1991 [19]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT	No significant difference between groups	Higher with soybean oil/MCT (142.3 ± 29.3 vs 132.1 ± 27.85 (mg/dL);p < 0.001)
Rubin et al., 1995 [20]	Premature infants (<35 wk)	Soybean oil vs PFE 4501 vs Soybean oil/ MCT	Significant increase from baseline in all groups. Soybean oil: 160.3±66.1 mg% vs. 53.7 ± 23.8 mg% (p<0.01). PFE: 150.4 ± 76.9 mg% vs. 51.2 ± 25.8 mg% (p<0.01). Soybean oil/MCT: 238.4 ± 72.3 mg% vs. 57.5 ± 34.3 mg% (p<0.001).	Increase from baseline in all groups with only soybean oil reaching statistical significance. Soybean oil: ~128 mg/dl vs. ~103 mg/dl; p<0.05 (estimated from graph). PFE: ~120 mg/dl vs. ~109 mg/dl (estimated from graph). Soybean oil/MCT: ~119 mg/dl vs. ~100 mg/dl (estimated from graph).
Smuts et al., 1999	VLBW infants	10% Soybean oil	No significant difference between	No significant difference between

[46]	(<1500 g, <32 weeks	(Lipovenous/LV) vs 10% Soybean oil (Intralipid /IL) vs 20% Soybean oil (Lipovenous/LV) vs 20% Soybean oil (Intralipid/IL)	groups	groups
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	No significant difference between groups	No significant difference between groups
Vlaardingerbroek et al., 2014 [29]	VLBW infants (birth weight <1500 g)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	No significant difference between groups
Webb et al., 2008 [43]	Neonates (≥25 wk of gestation <7 days of age)	Soybean oil vs Olive oil/Soybean oil	Lower in soybean oil group (0.7 ± 0.4 vs 1.0 ± 0.6 mmol/L no P value given)	Not reported

Table 8

Summary of key features and findings of studies investigating the effect of different lipid emulsions on liver enzymes and bilirubin

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on alanine transaminase (ALT, mg/dL)	Effect on aspartate transaminase (AST, mg/dL)	Effect on gamma-glutamyl transpeptidase (GGT, mg/dL)	Effect on total bilirubin (mg/dL)
Beken et al., 2013 [45]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	No significant difference between groups	Not reported	No significant difference between groups	No significant difference between groups
D'Ascenzo et al., 2014 [28]	ELBW infants (500 to 1249 g)	Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	No significant difference between groups
Demirel et al., 2011 [40]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	Not reported
Deshpande et al., 2009 [23]	Preterm infants (23 to <28 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	Not reported	No significant difference between groups	No significant difference between groups
Deshpande et al., 2014 [32]	Preterm infants (<30 wk)	Soybean oil/MCT/Olive oil/Fish oil vs Olive oil/ Soybean oil	Not reported	Not reported	Not reported	No significant difference between groups
Rubin et al., 1995 [20]	Premature infants (<35 wk)	Soybean oil vs PFE 4501 vs Soybean Oil/MCT	Not reported	Decrease was significant in the soybean oil and soybean oil/MCT groups (no p value given)	Not reported	Not reported
Göbel et al., 2003	Premature	Soybean oil vs	No significant	No significant	No significant	No significant difference

[42]	infants (28 to <37 wk)	Olive oil/ Soybean oil	difference between groups	difference between groups	difference between groups	between groups
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive oil/ Soybean oil vs Soybean oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	No significant difference between groups
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/ MCT vs Olive oil/ Soybean oil	Not reported	Not reported	No significant difference between groups	No significant difference between groups
Köksal et al., 2011 [44]	Premature infants (<34 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	No significant difference between groups
Lam et al., 2014 [26]	Neonates (age not given)	Soybean oil vs Fish oil	Lower rate of increase of ALT with fish oil blend (IU/L per week): 1.1 (-5.2 to 7.5) vs. 9.1 (4.1-14.1) p=0.02	Not reported	Not reported	Not reported
Nehra et al., 2014 [30]	Neonates and infants (<3 mo)	Soybean oil vs Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	No significant difference between groups
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/MCT/ Olive oil/Fish oil	No significant difference between groups	Not reported	No significant difference between groups	Lower in fish oil group (5.54 (3.99) group vs. 5.74 (4.37), p=0.049)
Savini et al., 2013 [36]	Preterm infants (500–1249 g)	Soybean oil vs Soybean oil/MCT Vs Soybean oil/ MCT/Fish oil vs Olive oil/ Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	No significant difference between groups	No significant difference between groups	No significant difference between groups
Skouroliakou et al., 2010 [33]	Premature infants	Soybean oil vs Soybean	Not reported	Not reported	Not reported	No significant difference between groups

	(<1500 g, <32 wk)	oil/MCT/ Olive oil/Fish oil				
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	Not reported	Higher in soybean oil group (188.8±177.7 IU/L vs. 107.8±81.7 IU/L; (p<0.05))	No significant difference between groups
Vlaardingerbroek et al., 2014 [29]	VLBW infants (birth weight <1500 g)	Soybean oil vs Soybean oil/MCT/Olive oil/Fish oil	No significant difference between groups	Higher in fish oil group (34.59 ± 24.46 oil group vs. 23.97 ± 9.90, p=0.027)	Not reported	No significant difference between groups

Table 9

Summary of key features and findings of studies investigating the effect of different lipid emulsions on markers of oxidative stress.

Author and year	Patient group (weight and age)	Lipid compounds compared	F2-isoprostanes (pmol/L)	Other markers
Deshpande et al., 2014 [32]	Preterm infants (<30 wk)	Soybean oil/MCT/ Olive oil/Fish oil Vs Olive oil/Soybean oil	Lower in fish oil group: 2051.7 (377.6) vs 2642.8 (738.6) (p=0.037)	Not reported
Deshpande et al., 2009 [23]	Preterm infants (23 to <28 wk)	Soybean oil vs Olive oil/Soybean oil	No significant difference between groups	Not reported
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/MCT vs Olive oil/ Soybean oil	Not reported	Plasma concentration of thiobarbituric acid reactive substances (TBARS) was not different between the groups
Köksal et al., 2011 [44]	Premature infants (<34 wk)	Soybean oil vs Olive oil/ Soybean oil	Not reported	Total antioxidant capacity in blood was not significantly different between groups
Roggero et al., 2010 [50]	Preterm infants (>700 g, 28–33 wk)	Soybean Oil Vs Olive oil/ Soybean Oil Vs Soybean Oil/MCT	No significant difference between groups	Not reported
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/ MCT/Olive oil/Fish oil	Not reported	Plasma malondialdehyde was not different between groups
Webb et al., 2008 [43]	Neonates (≥25 wk of gestation <7 days of age)	Soybean oil vs Olive oil/ Soybean oil	No significant difference between groups	Not reported

Table 10

Summary of key features and findings of studies investigating the effect of different lipid emulsions on blood and inflammatory markers

Author and year	Patient group (weight and age)	Lipid emulsions compared	Effect on blood count and related measures	Effect on inflammatory markers
Beken et al., 2013 [45]	VLBW infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	Haemoglobin, leucocytes and platelets were not significantly different between groups	Not reported
D'Ascenzo et al., 2011 [27]	ELBW infants (500 to 1249 g)	Soybean oil/MCT vs Soybean oil/ MCT/Fish oil	Haemoglobin, haematocrit, erythrocytes, leucocytes and platelets were not significantly different between groups	CRP was not significantly different between groups
D'Ascenzo et al., 2014 [28]	ELBW infants (500 to 1249 g)	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	Haemoglobin, haematocrit, erythrocytes, leucocytes and platelets were not significantly different between groups	Not reported
Deshpande et al., 2014 [32]	Preterm infants (<30 wk)	Soybean oil/MCT/ Olive oil/Fish oil vs Olive oil/ Soybean oil	Full blood cell counts were not significantly different between groups	CRP was not significantly different between groups
Gawecka et al., 2008 [41]	Premature infants (<1500 g, <32 wk)	Soybean oil vs Olive oil/Soybean oil	Not reported	Cytokine production by peripheral blood mononuclear cells (TNF-α, IL-10 and IL-6) did not differ between groups
Goulet et al., 1999 [24]	Children (1-9 yr)	Soybean oil vs Olive oil/ Soybean oil	Haemoglobin, haematocrit, erythrocytes, leucocytes and platelets were not significantly different between groups	Not reported
Hartman et al., 2009 [25]	Children (<18 yr)	Soybean oil/MCT vs Olive oil/ Soybean oil	No differences in the routine laboratory parameters including complete blood count between the two groups at baseline or follow-up.	Not reported

Lam et al., 2014 [26]	Neonates (age not given)	Soybean oil vs Fish oil	Haemoglobin, leucocytes and platelets were not significantly different between groups	Not reported
Larsen et al., 2012, 2015 [15,16]	Infants (age not given)	Soybean oil vs MCT/Soybean oil/ Fish oil	Not reported	The mean plasma concentration of TNF-α (p=0.02), IL-1β (p=0.03) and IL-6 (p=0.01) was lower in the fish oil group. Though not statistically significant, the ratios of pro- to anti-inflammatory cytokines were lower in the fish oil group. There was no difference in C reactive protein (CRP) between the groups
Magnusson et al., 1997 [21]	Neonates (up to and including 7 d)	Soybean oil vs PFE 4501	Haematological values were all within normal ranges.	Not reported
Nehra et al., 2014 [30]	Neonates and infants (< 3 mo)	Soybean oil Vs Fish oil	Haemoglobin, leucocytes and platelets were not significantly different between groups	Not reported
Rayyan et al., 2012 [34]	Premature infants (<34 wk)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	Haemoglobin, haematocrit, erythrocytes, leucocytes and platelets were not significantly different between groups	CRP was not significantly different in both groups
Skouroliakou et al., 2010 [33]	Premature infants (<1500 g, <32 wk)	Soybean oil vs Soybean oil/ MCT/ Olive oil/Fish oil	Haematocrit, leucocytes and platelets were not significantly different between groups	CRP was not significantly different in both groups
Tomsits et al., 2010 [35]	Premature infants (birth weight 1000–2500 g, 34 wk)	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	At study termination, soybean oil group had significantly higher levels of haemoglobin (122.10 ± 19.23 g/l vs. 109.46 ± 21.92 g/l), haematocrit (36.18 ± 5.80 % vs. 31.86 ± 6.41 %), erythrocytes (3.65 ± 0.62 10^{12}/l vs. 3.24 ± 0.63 10^{12}/l) compared to the fish oil blend ($p < 0.05$). Leucocytes and platelets were not significantly different between groups	CRP was not significantly different in both groups

Vlaardingerbroek et al., 2014 [29]	VLBW infants (birth weight <1500 g)	Soybean oil vs Soybean oil/ MCT/Olive oil/ Fish oil	Platelets were not significantly different between groups	Not reported

Supplementary Table 1

Search strategy

Population	**Parenteral Nutrition**	**Lipid**	**Clinical outcomes / laboratory parameters**
pediatric, paediatric	“parenteral nutrition”, PN	lipid	“nutrient status”
infant	“total parenteral nutrition”, TPN	fat*	height, length
child*	parenteral	“fatty acid”	weight, “weight gain”
preterm	intravenous	oil	growth
neonate	infusion	“medium chain triglycerides”, MCT	“fat percentage”
“very low birth weight”, “extremely low birth weight”, “low birth weight”, VLBW, ELBW		“long chain triglycerides”, LCT	“head circumference”
“new born”		triacylglycerol	neurodevelopment, “mental development”, neurocognitive
premature		“monounsaturated fatty acid”, MCT	“liver function”, “liver fat”
		“polyunsaturated fatty acid” PUFA	“blood lipids”
		“fish oil”, FO	“hospital stay”, “hospital duration”
		“olive oil”	infection
		soy, soybean	
		omega*	
		emulsion	
		Intralipid, ClinOleic, SMOFlipid	

Supplementary Table 2

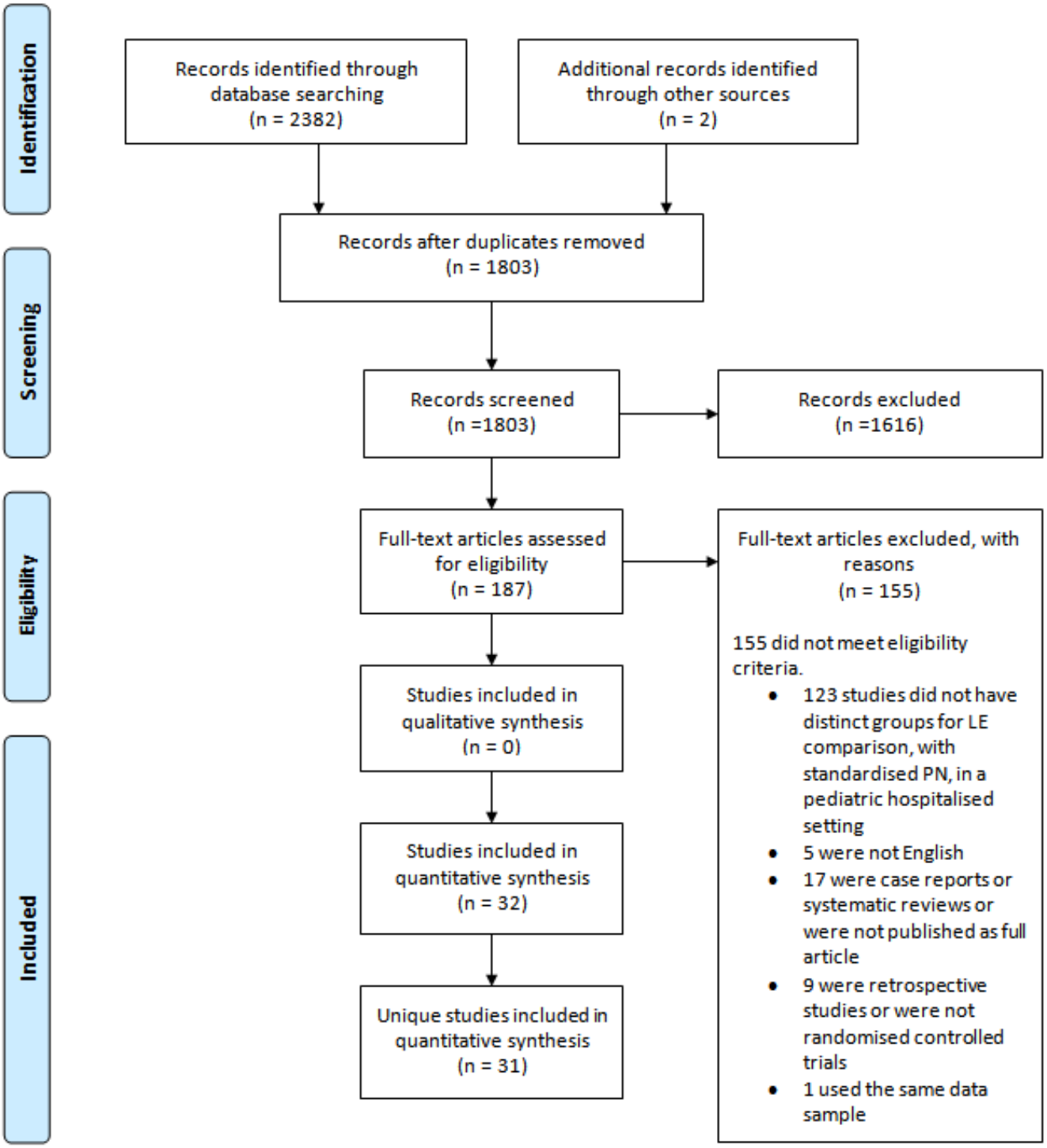
Study information extraction table

Studies			
Population			
Hospitalised			
Paediatric (<18yrs)			
Exposure			
IV lipid emulsion			
Outcomes			
Nutrient status			
Growth			
Development			
Lab and clinical outcomes			
Type of study			
Randomised controlled trials			
Non-randomised controlled trials			
Cohort study			
Action*			

Responses available: Y=yes, N=no, U=undecided

*Actions available: Y=fits criteria; included, N=excluded, U=paper needs to be fully read

Figure 1: PRISMA flow chart of study identification[6]



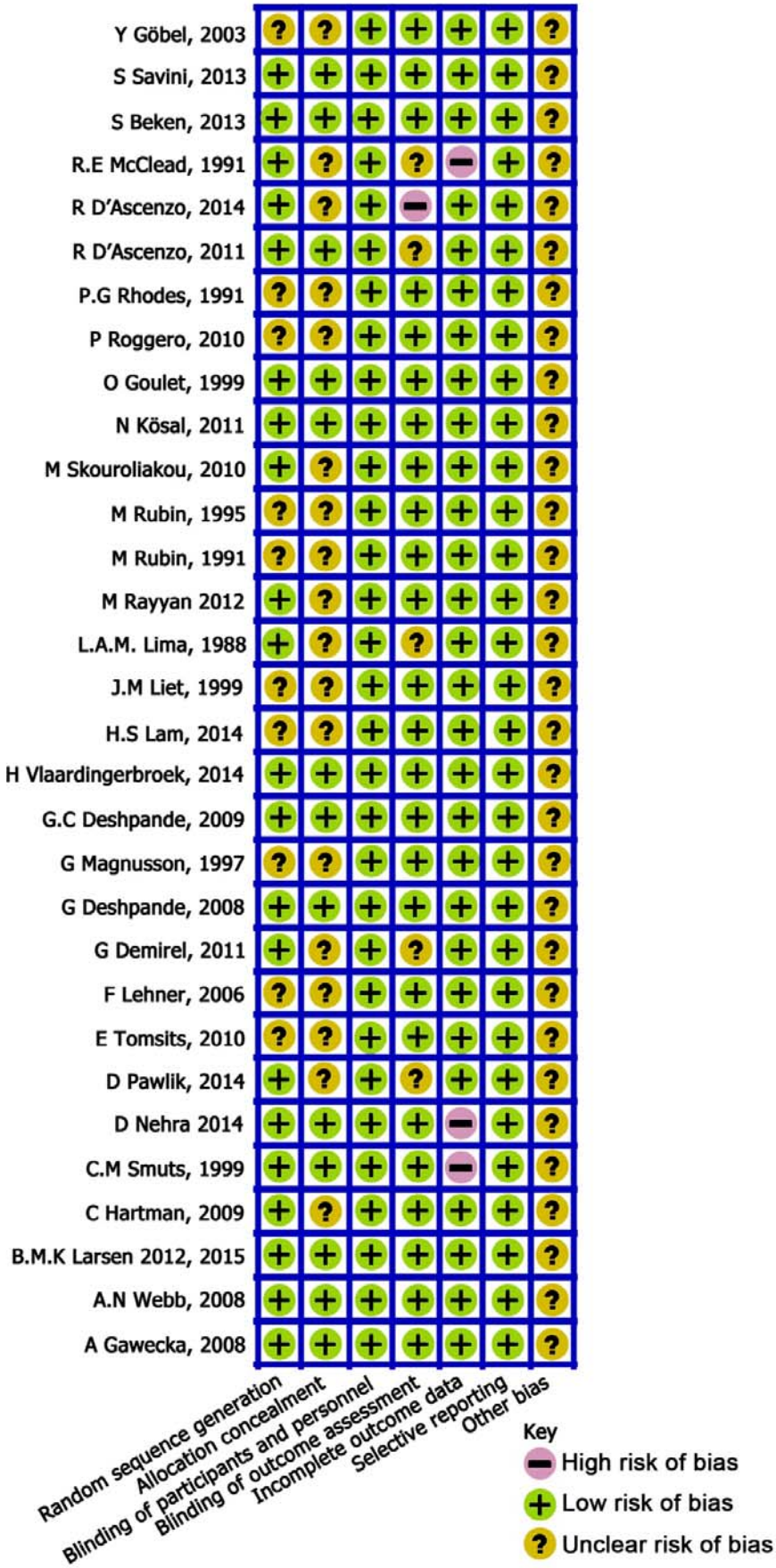


Figure 2. Sources of bias within each study determined using the Cochrane risk of bias tool.

Figure 3. Risk of bias: authors' judgements about category of bias presented as percentages across all included studies.