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CLINICAL GUIDELINES

Guidelines for parenteral nutrition in preterm infants: The American Society for Parenteral and Enteral Nutrition

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Abstract

Background: Parenteral nutrition (PN) is prescribed for preterm infants until nutrition needs are met via the enteral route, but unanswered questions remain regarding PN best practices in this population.

Methods: An interdisciplinary committee was assembled to answer 12 questions concerning the provision of PN to preterm infants. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process was used. Questions addressed parenteral macronutrient doses, lipid injectable emulsion (ILE) composition, and clinically relevant outcomes, including PNALD, early childhood growth, and neurodevelopment. Preterm infants with congenital gastrointestinal disorders or infants already diagnosed with necrotizing enterocolitis or PN-associated liver disease (PNALD) at study entry were excluded.

Results: The committee reviewed 2460 citations published between 2001 and 2023 and evaluated 57 clinical trials. For most questions, quality of evidence was very low. Most analyses yielded no significant differences between comparison groups. A multicomponent oil ILE was associated with a reduction in stage 3 or higher retinopathy of prematurity (ROP) compared to an ILE containing 100% soybean oil. For all other questions, expert opinion was provided.

Conclusion: Most clinical outcomes were not significantly different between comparison groups when evaluating timing of PN initiation, amino acid dose, and ILE composition. Future clinical trials should standardize outcome definitions to permit statistical conflation of data, thereby permitting more evidence based recommendations in future guidelines. This guideline has been approved by the ASPEN 2022-2023 Board of Directors.

KEYWORDS
amino acids, intensive care, lipids, neonatal intensive care, neonates, nutrition, parenteral nutrition, pediatrics, preterm, prematurity

PURPOSE

Parenteral nutrition (PN) is part of standard nutrition care for preterm neonates and infants (henceforth referred to as preterm infants) when estimated energy and nutrient requirements cannot be safely provided via the enteral route immediately after birth. While advances in PN formulations have led to safer admixtures, several questions remain as to how PN may mitigate adverse health outcomes.

The purpose of this guideline is to systematically evaluate the quality of relevant literature and provide recommendations on key clinical questions pertaining to the clinical practice of providing PN in preterm infants. The focus of this guideline is on preterm infants born without congenital diseases requiring surgery and does not address preterm infants who have been diagnosed with PN-associated liver disease (PNALD). This guideline's target population of preterm infants is expected to advance to full enteral nutrition without difficulty except in the event of necrotizing enterocolitis (NEC), an unpredictable complication associated with prematurity. The questions in this guideline address multiple aspects of PN, including the timing of PN initiation, nutrient dosing, and lipid injectable emulsion (ILE) composition. The a priori focus of the guideline was on the nutrients in PN; this guideline does not address aspects such as PN compounding and/or logistics of administration. This guideline serves as a foundation for future updates and systematic evaluation of additional relevant questions.

Recommendations in this guideline do not constitute medical or other professional advice and should not be taken as such. To the extent that the information published herein may be used to assist in the care of patients, the primary component of quality medical care is the result of the professional judgment of the healthcare professionals providing care. The information presented here is not a substitute or replacement for the exercise of professional judgment by healthcare professionals; rather, it is intended to supplement professional training and judgment. Circumstances and patient specifics in clinical settings may require actions different from those recommended in this document; in those cases, the judgment of the treating professionals should prevail. Use of this information does not in any way guarantee any specific benefit in outcome or survival. This guideline has been approved by the American Society for Parenteral and Enteral Nutrition (ASPEN) 2022–2023 Board of Directors.

An executive summary of guideline questions and recommendations is provided in Table 1.

TARGET POPULATION

The target population includes infants born preterm (birth prior to 37 weeks of gestation). Randomized controlled trials (RCTs) were included if they enrolled preterm infants without congenital gastrointestinal disorders who required PN. This includes preterm infants who were at risk for NEC and PNALD yet were not diagnosed with either at study entry. RCTs were excluded if they enrolled infants with congenital gastrointestinal disorders, congenital heart disease, short bowel syndrome, intestinal failure, and genetic or metabolic disorders or infants treated in pediatric intensive care units. Clinical trials of different ILE compositions needed to contain at least one group exposed to soybean oil (SO) ILE for consistent comparisons.

Target audience

The guidelines are intended for use by all healthcare providers involved in prescribing PN to preterm infants. These providers are primarily neonatal physicians, nurse practitioners, physician assistants, nurses, dietitians, pharmacists, and interdisciplinary nutrition support teams in neonatal intensive care units. Findings in this guideline are also expected to provide important considerations for pediatric gastroenterologists and surgeons.

Terminology, outcomes, and definitions

For this guideline, the term PN is inclusive of intravenous amino acids (AAs), dextrose, and ILE. With due attention to protein prescribing for preterm infants, crystalline AAs are directly infused into the patient. Therefore, the terminology utilized in these guidelines is AA, not protein. Importantly, where AA appears, this is referring to an age-appropriate, neonatal crystalline AA solution. For content relevant to ILE, this document utilizes either ASPEN-approved designations[4] to comment on a specific ILE (eg, an ILE composed of 100% SO is referred to as SO-ILE) or may refer to specific types of oils included in the ILE, such as SO or fish oil (FO). As this document does not address preterm infants who have been diagnosed with PNALD, the guideline does not include studies of an ILE composed of 100% FO. The questions address the entire PN mixture altogether or individual PN components. The term micronutrient refers to an individual nutrient required in relatively small amounts, often—but not always specified to be—vitamins and minerals. For the purposes of this guideline, single nutrients prescribed individually (eg, glutamine, carnitine) in a clinical trial with the purpose of assessing a specific outcome were also classified as micronutrients. In general, the studies assessed do not always specify the use of PN solutions immediately available at any hour, commonly referred to as “starter” or “stock” PN. Still, these solutions may have been utilized within a clinical trial to provide PN within hours of birth.

Outcome definitions were discussed, and agreement reached through group consensus. To be eligible for inclusion, clinical trials must have included at least one outcome consistent with these agreed-upon definitions. Clinical trials that did not specify definitions of relevant outcomes were not included.

Primary outcomes included measures of weight gain, linear growth, and head growth. Growth outcomes focused on clinically meaningful times (eg, age of 28 days, 36 weeks' postmenstrual age) as opposed to

TABLE 1 Twelve guideline questions and recommendations.

Questions and recommendations	Evidence/GRADE
Question 1: In preterm infants, compared with later initiation, does early initiation of PN macronutrients improve growth outcomes? *Recommendation*: We recommend prompt initiation of PN after birth as soon as appropriate vascular access is obtained. However, few studies evaluated the timing of PN initiation (inclusive of dextrose, AA, and ILE) in preterm infants using growth outcomes that met definitions for inclusion.	Quality of evidence: Very low Strength of recommendation: Strong
Question 2: In preterm infants, compared with lower doses of parenteral AA, do higher doses of parenteral AA improve growth outcomes? *Recommendation*: We recommend against an initial dose of >3 g/kg/day given that a single trial found an increased rate of sepsis in infants who were prescribed an initiating AA dose of 3.5 g/kg/day. In considering the maximal target dose, we recommend providing parenteral AA at a minimum of 3 g/kg/day and not exceeding 3.5 g/kg/day. This guidance accounts for growth outcomes as well as neurodevelopmental outcomes associated with AA dose as addressed in question 3. Also, current evidence remains limited in distinguishing any benefit—namely, improved growth—comparing a maximum AA dose of 3.5 vs 4 g/kg/day.	Quality of evidence: Low Strength of recommendation: Strong
Question 3: In preterm infants, compared with lower doses of parenteral AA, do higher doses of parenteral AA improve neurodevelopmental outcomes? *Recommendation*: In considering the maximal target dose, we recommend providing parenteral AA doses at a minimum of 3 g/kg/day without increasing beyond 3.5 g/kg/day. The current evidence remains limited in distinguishing any benefit—namely, improved neurodevelopment—comparing a maximum AA dose of 3.5 vs 4 g/kg/day, and there is the suggestion that exceeding 3.5 g/kg/day may not be without harm.	Quality of evidence: Low Strength of recommendation: Strong
Question 4: In preterm infants, compared with lower ILE doses, do higher ILE doses improve growth outcomes? *Recommendation*: To improve growth, we recommend daily advancement of ILE to a dose of 3 g/kg/day if using SO-ILE or multicomponent ILE. We strongly emphasize the need for attention to ILE composition when making decisions on ILE dose to ensure the provision of sufficient fatty acids for the purposes of preventing an essential fatty acid deficiency (EFAD). Providing suboptimal ILE doses that are associated with a risk for an EFAD may impair growth and increase the risk for other adverse outcomes.	Quality of evidence: Very low Strength of recommendation: Strong
Question 5: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, is altering the ILE composition by reducing the proportion of SO associated with growth outcomes? *Recommendation*: At this time, we do not recommend any specific ILE composition for enhanced growth, given there was no evidence of benefit from any particular ILE.	Quality of evidence: Very low Strength of recommendation: Strong
Question 6: In preterm infants, compared with a higher dose of macronutrients (AA, dextrose, ILE), does a lower dose of macronutrients reduce incidence of PNALD? *Recommendation*: We do not recommend routinely reducing the dose of AA, dextrose, or ILE when providing PN to preterm infants for the purposes of preventing PNALD.	Quality of evidence: Very low Strength of recommendation: Strong
Question 7a: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, does a reduction in SO using any multicomponent-oil ILE reduce the incidence of PNALD? *Recommendation*: For the purpose of preventing PNALD in preterm infants, we do not recommend any specific ILE composition. We found no evidence of reduced PNALD risk with any specific ILE, whether it contains 100% SO as the sole oil source or a multicomponent-oil ILE with or without FO. *Question 7b: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, does reducing SO using a multicomponent-oil ILE that includes FO reduce the incidence of PNALD?* *Recommendation*: For the purposes of preventing PNALD in preterm infants, we do not recommend the use of any specific ILE, whether it contains 100% SO as the sole oil source or a multicomponent-oil ILE that includes FO. As identified in secondary analyses, further study is needed to evaluate the potential for an ILE containing FO and its association with ROP severity.	Quality of evidence: Low Strength of recommendation: Strong
Question 8: In preterm infants, does reducing the dose of ILE reduce levels of unbound bilirubin? *Recommendation*: We are unable to recommend any specific ILE dose for the purpose of reducing unbound bilirubin levels. We suggest further research utilizing clinical trials is needed to address this question.	Quality of evidence: Very low Strength of recommendation: Strong
Question 9: In preterm infants, does a reduced dose of ILE reduce the risk of sepsis? *Recommendation*: We recommend against a dose reduction of ILE to prevent sepsis.	Quality of evidence: Very low Strength of recommendation: Strong
Question 10: In preterm infants, does providing parenteral micronutrients improve growth outcomes and reduce the risk for morbidities?	Quality of evidence: Very low Strength of recommendation: Strong

TABLE 1 (Continued)

Questions and recommendations	Evidence/GRADE
Recommendation: Given the paucity of available data from clinical trials, we recommend that micronutrient provisions, including calcium and phosphate prescribing, be in accordance with doses advised in consensus guidelines such as those provided by ASPEN and ESPGHAN.[1–3]	
Question 11: In preterm infants, compared with customized PN solutions, are standardized PN solutions associated with growth outcomes? *Recommendation*: Given the absence of clinical trials to evaluate this question, we do not recommend use of standardized PN solutions for routine care of preterm infants. This recommendation does not address or dissuade use of premade PN solutions generally utilized for the first 24 h after birth (commonly referred to as "starter" or "stock" PN), which are useful given their immediate availability at all hours.	Quality of evidence: Very low Strength of recommendation: Strong
Question 12: In preterm infants, does the use of insulin improve growth outcomes? *Recommendation*: We recommend against the routine use of insulin for the purposes of improving growth outcomes in hospitalized preterm infants.	Quality of evidence: Very low Strength of recommendation: Strong

Abbreviations: AA, amino acid; ASPEN, American Society for Parenteral and Enteral Nutrition; EFAD, essential fatty acid deficiency; ESPGHAN, European Society for Paediatric Gastroenterology Hepatology and Nutrition; FO, fish oil; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ILE, lipid injectable emulsion; PN, parenteral nutrition; PNALD, PN-associated liver disease; ROP, retinopathy of prematurity; SO, soybean oil.

measurements conducted at a specific time during a trial (eg, study day 7). Acceptable growth assessments included both cross-sectional measures (eg, weight at 36 weeks' postmenstrual age) and those that provided rates of change (eg, g/kg/day, g/day, cm/week). Neurodevelopmental outcomes included cross-sectional measures at 6, 12, 18, and 24 months' corrected age, reflecting the most common duration of follow-up in clinical trials, assessed with any validated instrument. The most common instrument utilized in trials was the Bayley Scales of Infant Development (BSID), 2nd and 3rd editions. Other scales would have been considered if they were utilized in relevant trials. Trials measuring PNALD, primarily documented as cholestasis, were included if the diagnostic threshold for PNALD was a serum direct or conjugated bilirubin concentration of >2 mg/dl (34 µmol/L) or >1.5 mg/dl (>26 µmol/L). This decision was made considering the wide range of PNALD definitions utilized in clinical trials and with the goal of conflating consistent outcomes. A complete listing of outcomes and definitions is detailed in Supporting Information: Table 1.

Most prematurity-associated morbidities and other clinically important outcomes were evaluated as secondary outcomes. These outcomes included high-grade intraventricular hemorrhage (IVH; inclusive of grade 3 or 4, unilateral or bilateral), NEC (Bell's stage 2 or higher), bronchopulmonary dysplasia (BPD; supplemental O_2 therapy at 36 weeks' postmenstrual age), sepsis (any positive culture from a sterile site including blood, urine, or cerebrospinal fluid), retinopathy of prematurity (ROP; stage 3 or greater or any treatment including photocoagulation or intravitreal injections of antivascular endothelial growth factor), length of hospital stay, and mortality. Additional biochemical outcomes included hypertriglyceridemia, hyperglycemia, and blood urea concentrations.

Secondary outcomes were not considered any less important than the primary outcomes. These outcomes, except for sepsis in question 9, were not prioritized in the development of questions yet were able to be assessed during data abstraction. For each question in this guideline, assessments of the primary outcomes are discussed first as "rationale for recommendation." Subsequently, any trials measuring secondary outcomes are discussed in a separate section entitled "Secondary outcomes," which immediately follows the rationale for recommendation.

METHODS

A task force composed of interdisciplinary experts of ASPEN, including neonatologists, a gastroenterologist, a neonatal dietitian, a neonatal pharmacist, and a guideline methodologist/epidemiologist, was created. The task force defined the literature search keywords, developed 12 key clinical questions that addressed major practice themes, and determined the period for the literature search, target population, and outcomes to be addressed. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) process was used to create these guideline recommendations.[5] A bias panel composed of three researchers (DDC, JM, and LM) assessed bias in the included studies (Supporting Information: Figure 1). Bias was assessed using the Risk of Bias 2 assessment tool from the Cochrane Group (Supporting Information: Tables 2–5).[6]

Literature search and data acquisition

A search in PubMed/MEDLINE and Embase databases from 2001 to 2023 was conducted to identify RCTs published in English that answered guideline questions. Titles and abstracts from those citations were scanned for potential relevance to the research questions. For a selected study to be fully reviewed, the manuscript was downloaded, and the entire document was examined for relevance. For each study that met inclusion criteria, two team members assessed the study and abstracted prespecified data using a standardized data collection form. For each study, if any discrepancy in data abstracted existed between the two reviewers, either the discrepancy was discussed between those two reviewers and agreement determined or a third review of that data was

<table>
<tr><th>Category A
Infant Terms</th><th colspan="2">Category B
Nutrition Terms</th><th>Category C
Further Restrictions</th></tr>
<tr><td rowspan="3">MeSH Terms:
"Infant, Newborn, Diseases", "Infant, Newborn"

Text Terms:
"Infant", "Neonate", "Very low birth weight", "Extremely low birth weight", "Low birth weight", "premature", "Preterm", "Prematurity", "Small for gestational age"</td><td colspan="2">MeSH Terms:
"Parenteral Nutrition", "Parenteral Nutrition Solutions", "Infant Nutritional Physiological Phenomena", "Micronutrients", "Minerals", "Insulins", "Carnitine"

Excluded MeSH Terms:
"Bottle Feeding", "Breast Feeding", "Weaning"</td><td rowspan="3">MeSH Terms:
Humans

Period: 2001- 2023

Publication Type:
Clinical Trials</td></tr>
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Nutrition Terms</td><td>Category B2
Nutrition Terms</td></tr>
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</table>

FIGURE 1 Search terms utilized for literature searches in PubMed/MEDLINE and Embase. MeSH, Medical Subject Heading.

TABLE 2 Specifications for quality of evidence and considerations for determining strength of recommendations.

Quality of evidence	Weighing risks vs benefits	Strength of recommendation	Clinical guideline statement
High to very low	Net benefits outweigh harms	Strong	We recommend
High to very low	Trade-offs for patient are important	Weak	We suggest

performed for final determination. Figure 1 shows the PubMed/MEDLINE and Embase search strategy.

Assessment of evidence quality

The GRADE process was used to determine the evidence quality and strength of the recommendation (Table 2). The GRADE process distinctly separates the quality of the evidence from the strength of the recommendation statements. Evidence quality describes the ability of the available evidence to answer the population, intervention, control, and outcomes (PICO) question, while recommendation strength describes the clinical panel's assessment of the potential harms vs potential benefits of the recommendation independent of the evidence quality. Thus, a recommendation may be "strong" despite comparatively weak published evidence if the net benefits outweigh the harms from its adoption. Recommendations based mainly on expert opinion are deemed weak.

Evidence tables and forest plots were used to develop practical recommendations for each question with the GRADE methodology. The recommendations for questions are summarized in Table 1. Tables 3–12 summarize the evidence information of trials related to each guideline question.

Statistical analysis

When three or more comparable studies reported on any individual outcome, random-effects summary statistics with forest plots were generated for that outcome. Forest plots report the mean differences (MDs) with 95% CIs for continuous outcomes and risk differences with 95% CIs for dichotomous outcomes. Forest plots with 10 or more studies prompted testing for publication bias.

RESULTS

The PubMed/MEDLINE and Embase searches identified 2460 citations. After reviewing the titles and abstracts of those citations, 138 citations were identified for a complete assessment. Two reviewers examined each of those citations in full to determine eligibility for inclusion in the

TABLE 3 Clinical trial summary for question 1: In preterm infants, compared with later initiation, is early initiation of PN macronutrients associated with growth outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or median (25th–75th %)
Dongming[7]	Starting PN with dextrose, AA, and ILE (1.5 g/kg/day AA and ILE) within 24 h after birth and advanced to 3 g/kg/day vs initiation of dextrose only and PN initiation at 3 days.	GA < 34 weeks and BW < 1500 g Early: *n* = 40 Late: *n* = 40	Days to regain BW: 8.2 ± 2.4; 11.6 ± 3 Maximum weight loss from BW, %: 7.7 ± 1.5; 10.6 ± 3.3[b]
Heimler[5]	Starting AA 1.5 g/kg/day in first 24 h and increased to goal of 2.5 g/kg/day by day 3 vs starting AA on day 3 and increasing AA to goal of 2.5 g/kg/day by day 7. ILE was initiated on day 4 for both groups.	GA < 34 weeks and AGA Early maximum dose: *n* = 8 Later maximum dose: *n* = 9	Days to regain BW: 12 ± 3.2; 13.7 ± 2.7
Te Braake[6]	Comparison AA 2.4 g/kg/day for days 1–4 vs no AA on day 1, 1.2 g/kg/day on day 2; then, 2.4 g/kg/day ILE was initiated on day 2 for both groups.	BW ≤ 1500 g Early AA: *n* = 66 Later AA: *n* = 69	Days to regain BW: 8 (2–25); 10 (2–26)

Abbreviations: AA, amino acid; AGA, appropriate for gestational age; BW, birth weight; GA, gestational age at birth; ILE, lipid injectable emulsion; PN, parenteral nutrition.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

guideline. This resulted in 57 clinical trials that fulfilled the inclusion criteria, addressed at least 1 or more of the 12 preidentified key questions, and included outcomes that were described clearly and were consistent with those accepted for inclusion.

Question 1: In preterm infants, compared with later initiation of PN, does early initiation of PN macronutrients improve growth outcomes?

Recommendation: We recommend prompt initiation of PN after birth as soon as appropriate vascular access is obtained. However, few studies evaluated the timing of PN initiation (inclusive of dextrose, AA, and ILE) in preterm infants using growth outcomes that met definitions for inclusion.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: Trials included in this analysis delayed PN initiation by 1–3 days after birth and evaluated short-term growth outcomes, including days to regain birth weight (BW)[7–9] and percent maximum weight loss as a percentage of BW (Table 3). Given the variability in reporting growth outcomes and the measures of central tendency, a combined analysis could not be performed. One single study with 40 infants in each group reported a significantly smaller postnatal weight loss as a percentage of BW with earlier initiation of AA and ILE.[7] The implications of a smaller weight loss are not known, particularly with a lack of long-term follow-up. Despite the very low quality of the evidence to answer our question, given the endogenous capacity to metabolize parenteral nutrients and that preterm infants rapidly accrue protein and total energy deficits after birth,[54] it is recommended to initiate PN promptly after birth in preterm infants.

Secondary outcomes

One trial evaluated mortality associated with early vs delayed (up to 48 h) parenteral AA initiation.[55] The trial identified no difference in mortality between groups (Supporting Information: Table 6).

Question 2: In preterm infants, compared with lower doses of parenteral AA, do higher doses of parenteral AA improve growth outcomes?

Recommendation: We recommend against an initial dose of >3 g/kg/day, given that a single trial found an increased rate of sepsis in infants who were prescribed an initiating AA dose of 3.5 g/kg/day. In considering the maximal target dose, we recommend providing parenteral AA at a minimum of 3 g/kg/day and not exceeding 3.5 g/kg/day. This guidance accounts for growth outcomes as well as neurodevelopmental outcomes associated with AA dose as addressed in question 3. Also, current evidence remains limited in distinguishing any benefit, namely improved growth, comparing a maximum AA dose of 3.5 vs 4 g/kg/day.

Quality of evidence: Low

Strength of recommendation: Strong

Rationale for recommendation: Initial AA doses varied in the clinical trials reviewed as did the maximum target doses (Table 4). Initial doses investigated were as low as 0.5–1 g/kg/day, which would be expected to keep preterm infants in a net negative nitrogen balance.[11,13,15,18,23,56] The maximum doses in lower-AA groups ranged from 2.5 to 3.5 g/kg/day, and maximum doses in higher-AA groups ranged from 3 to 4.5 g/kg/day. Only one study specifically targeted an AA dose of >4 g/kg/day,[19] although infants in another trial did receive AA doses >4 g/kg/day based on the study protocol intending to provide an additional 1 g/day in the intervention

TABLE 4 Clinical trial summary for question 2: In preterm infants, compared with lower doses of parenteral AA, are higher doses of parenteral AA associated with growth outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or median (25th–75th %)
Balakrishnan[10]	Start at AA at 3–4 vs 1–2 g/kg/day; both groups advanced to 4 g/kg/day	GA 24–30 weeks and BW 400–1250 g High AA: *n* = 85 Low AA: *n* = 83	Days to regain BW: 11.2 ± 5.2; 12.2 ± 5.4 Wt at 36 weeks/dc, g: 2128 ± 311; 2212 ± 389 WASDS at 36 weeks/dc: −1.41 ± 0.75; −1.23 ± 0.9 Length at 36 weeks/dc, cm: 42.6 ± 2.8; 43.7 ± 2.6 LASDS at 36 weeks/dc: −1.68 ± 1.07; −1.24 ± 1.02[b] HC at 36 weeks/dc, cm: 31.3 ± 1.2; 31.6 ± 1.6 HCSDS at 36 weeks/dc: −0.88 ± 0.75; −0.67 ± 0.97
Balasubramanian[11]	Start at AA at 3 vs 1 g/kg/day; both groups advanced to 4 g/kg/day	Inborn infants with BW 900–1250 g Higher AA: *n* = 60 Lower AA: *n* = 63	Days to regain BW: 16 (11–20); 12 (10–14)[b] Wt at 28 days, g: 1371 ± 202; 1494 ± 224[b] Length at 28 days, cm: 39.19 ± 1.8; 40.21 ± 2.34[b] HC at 28 days, cm: 28 (27–29); 29 (27.5–30.5) GV at first 28 days, g/kg/day: 8.67 ± 4.28; 13.15 ± 5.25[b] ΔLength birth to 28 days, cm/week: 0.36 ± 0.348; 0.63 ± 0.36[b] HC velocity birth to 28 days, cm/week: 0.25 (0.03–0.59); 0.625 (0.37–0.875)[b]
Bellagamba[12,c]	Comparison of maximum AA 3.5 g/kg/day vs maximum 2.5 g/kg/day; both groups started AA at 1.5 g/kg/day	BW 500–1249 g High dose: *n* = 82 Low dose: *n* = 82	Days to regain BW: 12.7 ± 5; 12.2 ± 5.1 Maximum Wt loss, %: 13.6 ± 6.2; 12.3 ± 5.5 Wt at 36 weeks/dc: 1936 ± 299; 1958 ± 345 WASDS at 36 weeks/dc: −1.73 ± 0.73; −1.68 ± 0.85 WASDS at 2 years: −0.09 ± 0.96; −0.10 ± 1.31 Length at 36 weeks/dc: 42.7 ± 2.3; 42.8 ± 2 LASDS at 36 weeks/dc: −1.74 ± 0.88; −1.7 ± 0.8 LASDS at 2 years: 0.66 ± 1.02; 0.79 ± 1.34 HC at 36 weeks/dc: 30.6 ± 1.2; 30.8 ± 1.6 HCSDS at 36 weeks/dc: −1.49 ± 0.83; −1.39 ± 1.14 HCSDS at 2 years: −1.01 ± 1.42; 0.94 ± 1.39
Blanco[13]	Starting AA 2 g/kg/day and maximum 4 g/kg/day vs starting AA 0.5 g/kg/day and maximum 3 g/kg/day in the first week	GA > 24 weeks and BW < 1000 g Higher dose: *n* = 16 with long-term follow-up Lower dose: *n* = 16 with long-term follow-up	GV at first 28 days, g/kg/day: 10.8 ± 4.2; 12.2 ± 4.6
Bloomfield[14]	Additional AA 1 g/day for 5 days administered through umbilical arterial catheter vs 0.45% saline administered through umbilical arterial catheter; baseline AA dose in PN was not influenced by protocol *Note*: different sites used varying ILE, and this was not part of the protocol	BW < 1000 g Higher dose: *n* = 217 Lower dose: *n* = 217	Wt at 36 weeks, g: 2440 ± 423; 2372 ± 413 Wt at dc, g: 3506 ± 851; 3374 ± 718 WASDS at 36 weeks: −0.65 ± 0.95; −0.68 ± 0.98 WASDS at 2 years: −0.24 ± 1.09; −0.05 ± 1.14 ΔW SDS birth to 36 weeks: −0.6 ± 0.78; −0.57 ± 0.88 ΔW SDS birth to dc: −0.59 ± 0.92; −0.66 ± 0.92 HC at 36 weeks, cm: 31.3 ± 1.6; 31.1 ± 1.5 HC dc, cm: 34.8 ± 2.3; 34.6 ± 1.9 HCSDS at 36 weeks: −0.88 ± 1; −0.93 ± 1.01 HCSDS at 2 years: −0.09 ± 1.21; 0.13 ± 1.4 ΔHC SDS birth to 36 weeks: −0.94 ± 0.93; −0.86 ± 1.08 ΔHC SDS birth to dc: −0.54 ± 1.05; −0.49 ± 1.03 Length at 36 weeks, cm: 43.8 ± 3; 43.4 ± 2.6 Length dc, cm: 49.2 ± 4.1; 48.8 ± 3.5 LASDS at 36 weeks: −1.34 ± 1.02; −1.32 ± 1.17 LASDS at 2 years: −0.41 ± 1.18; −0.55 ± 1.07 ΔLSDS birth to 36 weeks: −1.2 ± 1.23; −1.15 ± 1 ΔLSDS birth to dc: −1.11 ± 1.19; −1.11 ± 1.12
Bulbul[15]	Starting and maximum AA 3 g/kg/day vs starting 0.5 g/kg/day with advancement to 3 g/kg/day	GA 32 weeks, BW 750–1500 g and AGA	Days to regain BW: 12.5 ± 5.4; 10.2 ± 3.9 Wt at 36 weeks/dc, g: 2210 ± 91; 2155 ± 180 HC at 36 weeks/dc, cm: 32.1 ± 2.3; 31.2 ± 2.1

TABLE 4 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or median (25th–75th %)
		Earlier, higher dose: *n* = 22 Lower dose: *n* = 22	
Burattini[16]	Start AA at 1.5 g/kg/day advanced to maximum 2.5 g/kg/day vs starting AA 2.5 g/kg/day with advance to maximum 4 g/kg/day	BW 500–1249 g Higher dose: *n* = 56 Lower dose: *n* = −58	Days to regain BW: 11.2 ± 4.5; 11.7 ± 4.1 Maximum wt loss, %: 11.3 ± 5.2; 11.3 ± 5.0 Wt at 36 weeks/dc, g: 1865 ± 387; 1847 ± 387 WASDS at 36 weeks/dc: −1.88 ± 0.93; −1.95 ± 0.8 WASDS at 2 years: −0.22 ± 1.31; −0.17 ± 1.12 Length at 36 weeks/dc, cm: 42.7 ± 2.4; 42.7 ± 1.9 LASDS at 36 weeks/dc: −1.82 SD 0.91; −1.86 SD 0.76 LASDS at 2 years: 0.61 ± 1.25; 0.57 ± 1.12 HC at 36 weeks/dc, cm: 30.5 ± 1.4; 30.6 ± 1.3 HCSDS at 36 weeks/dc: −1.59 ± 0.88; −1.53 ± 0.9 HCSDS at 2 years: −0.57 ± 1.2; −0.56 ± 1.3
Can[17]	Start AA at 3 g/kg/day, advanced to 4 g/kg/day, with ILE starting at 2 g/kg/day, advanced to 3 g/kg/day by second day vs start AA 1.5 g/kg/day, advanced to 4 g/kg/day, with ILE starting at 1 g/kg/day, advanced to 3 g/kg/day by fourth day	GA 27–33 weeks and AGA Earlier, higher AA and ILE doses: *n* = 25 Lower doses: *n* = 25	Days to regain BW: 12.7 ± 2.8; 14.2 ± 3.0 Wt at 40 weeks, g: 3180 ± 474; 2992 ± 445
Clark[18]	Start AA at 1.5 g/kg/day advanced to 3.5 g/kg/day vs starting AA 1 g/kg/day advanced to 2.5 g/kg/day	GA 23–29 weeks and inborn Higher AA dose: *n* = 64 Lower AA dose: *n* = 58	Wt at 28 days, g: 1276 (1079–1629); 1170 (973–1559) Length at 28 days, cm: 38 (35.9–41); 37.2 (35–41) HC at 28 days, cm: 27.5 (25–28.5); 27 (24.7–29.4) GV first 28 days, g/kg/day: 12.9 (9.4–14.9); 11.4 (7.2–14.9) ΔLength birth to 28 days, cm/week: 0.8 (0.5–0.9); 0.8 (0.4–1.1) HC birth to 28 days cm/week: 0.5 (0.3–0.8); 0.5 (0.3–0.7)
Li[19]	Starting AA 1.8–2.5 g/kg/day advanced to 4–4.5 g/kg/day vs starting AA 1–1.5 g/kg/day advanced to 3.5 g/kg/day	GA <37 weeks and BW < 2500 g Higher AA: *n* = 110 Lower AA: *n* = 81	Days to regain BW: 6.36 ± 4.88; 8.48 ± 9.27[b]
Morgan[20]	Maximum AA and ILE 3.8 g/kg/day with dextrose 15.6 g/kg/day vs maximum AA and ILE 2.8 g/kg/day with dextrose of 13.5 g/kg/day Both groups used SO-ILE, and starting doses were AA 1.8 g/kg/day and ILE 1 g/kg/day	GA <29 weeks and BW < 1200 g Higher doses: *n* = 74 Lower doses: *n* = 76	Wt at 28 days, g: 1269 ± 222; 1212 ± 242 Wt at 36 weeks/dc, g: 2082 ± 293; 1976 ± 346 WASDS at 36 weeks/dc: −1.41 ± 0.72; −1.68 ± 0.88 ΔW SDS birth to 28 days: −1.05 ± 0.71; −1.19 ± 0.75 ΔW SDS birth to 36 weeks: −1.41 ± 0.72; −1.68 ± 0.88 HC at 28 days, cm: 27.1 ± 1.6; 26.5 ± 1.7 HC at 36 weeks/dc, cm: 31.6 ± 1.3; 31.1 ± 1.5[b] HCSDS at 36 weeks/dc: −0.93 ± 1.06; −1.32 ± 1.18[b] ΔHC first 28 days: 3.1 ± 0.9 cm/month; 2.6 ± 0.9 cm/month[b] ΔHC SDS birth to 28 days: −1.51 ± 0.87; −1.81 ± 0.86 ΔHC SDS birth to 36 weeks: −0.93 ± 0.1.06; −1.32 ± 1.18[b]
Scattolin[21]	Starting AA 2 g/kg/day advanced to 4 g/kg/day vs starting AA 1.5 g/kg/day advanced to 3 g/kg/day	BW < 1250 g Higher AA: *n* = 60 Lower AA: *n* = 55	Days to regain BW: 14.82 ± 5.77; 16.15 ± 7.25 Maximum wt loss, %: 12.76 ± 5.96; 12.25 ± 5.93 Wt at 36 weeks/dc, g: 1958.41 ± 269.25; 1786.64 ± 292.6[b] Length at 36 weeks/dc, cm: 43.06 ± 2.19; 42.03 ± 2.19[b] HC at 36 weeks/dc, cm: 30.85 ± 1.34; 30.71 ± 1.94
Strommen[22]	Compare starting AA 3.5 vs 2 g/kg/day	BW < 1500 g Higher AA: *n* = 23 Lower AA: *n* = 21	Days to regain BW: median 7; median 10[b] (no measure of variance reported)

(Continues)

TABLE 4 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or median (25th–75th %)
Tagare[23]	Comparison of AA 3 g/kg with SO-ILE 2 g/kg vs starting AA 1 g/kg advanced to 2 g/kg with ILE starting on day 3 at 1 g/kg/day without increase	GA <37 weeks and BW < 1500 g Higher doses: *n* = 17 Lower doses: *n* = 17	Days to regain BW: 9.5 ± 6.7; 11.5 ± 6.7
Tan[25]	Comparison of effect from PN with 20% more energy using starting AA and ILE at 1 g/kg/day, both advanced to 4 g/kg/day (117 kcal/kg/day) vs advancement to target of 3 g/kg/day for AA and ILE (93 kcal/kg/day)	GA <29 weeks Higher doses: *n* = 68 Lower doses: *n* = 74	Days to regain BW: 10.3 ± 6.3; 13.9 ± 6.3[b] Wt at 36 weeks/dc, g: 2136 ± 345; 2090 ± 293 WASDS at 36 weeks/dc: −1.3 ± 0.9; −1.4 ± 0.8 Length at 36 weeks, cm: 42.9 ± 2.3; 42.4 ± 2.1 LASDS at 36 weeks/dc: −2.3 ± 1.3; −2.6 ± 1.2 HC at 36 weeks/dc, cm: 31.1 ± 1.5; 31.4 ± 1.3 HCSDS at 36 weeks/dc: 1.0 ± 1.2; −0.8 ± 1.1
Vlaardingerbroek[25]	Comparison of effect of higher vs lower AA and early vs delayed ILE Group 1: Immediate start of AA 2.4 g/kg/day with ILE started at 2 g/kg/day advanced to 3 g/kg/day Group 2: Immediate start of AA 3.6 g/kg/day with ILE started at 2 g/kg/day advanced to 3 g/kg/day Group 3: Immediate start of AA 2.4 g/kg/day; SO-ILE started on second day at 1.4 g/kg/day advanced to 2.8 g/kg/day *Note*: Infants in Groups 1 and 2 exposed to ILE with SO,MCT,OO,FO-ILE or SO-ILE	BW < 1500 g Group 1: *n* = 49 Group 2: *n* = 47 Group 3: *n* = 48	GV first 28 days, g/kg/day: 13.4 ± 4.7;12.3 ± 5.8; 13.1 ± 5.7 GV through dc or 40 weeks, g/kg/day:25.0 ± 5.2; 27.0 ± 7.3; 25.8 ± 8.1 ΔWASDS birth to DOL 28: −1.3 ± 1.0; −1.5 ± 1.1; −1.3 ± 1.1 ΔWASDS birth to 40 weeks' PMA or dc: −0.3 ± 1.2; −0.03 ± 1.3; −0.1 ± 1.4 HC velocity birth to 28 days, cm/week: 0.57 ± 0.29; 0.59 ± 0.24; 0.66 ± 0.37 HC velocity birth to dc, cm/week: 0.81 ± 0.15; 0.84 ± 0.13; 0.83 ± 0.13 ΔHCSDS birth to 28 days: −0.9 ± 0.9; −0.9 ± 0.9; −0.6 ± 1.2 ΔHCSDS birth to 40 weeks or dc: 0.2 ± 1.0; 0.6 ± 1.1; 0.5 ± 1.0

Abbreviations: AA, amino acid; BW, birth weight; dc, discharge; FO, fish oil; DOL, day of life; GA, gestational age at birth; GV, growth velocity; HC, head circumference; HCSDS, head circumference–for-age standard deviation score; ILE, lipid injectable emulsion; LASDS, length-for-age standard deviation score; LSDS, length standard deviation score; MCT, medium-chain triglyceride; OO, olive oil; PMA, postmenstrual age; PN, parenteral nutrition; SDS, standard deviation score; SO, soybean oil; WASDS weight-for-age standard deviation score; Wt, weight; ΔL, change in length; ΔW, change in weight.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

[c]Clinical trials also included enteral supplementation of protein.

group.[14] Sufficient data allowed combined analysis for short-term measures (eg, time to regain BW) as well as later outcomes at discharge and postdischarge.[10,12,14,16,19] Collectively, a combined analysis allowed for evaluating at least one measure of all three parameters of weight gain and linear and head growth. In these combined analyses, which collectively evaluate initial and maximum doses, no growth outcome was significantly improved with higher vs lower AA doses (Figures 2–12).

In the first postnatal days, the maximum percentage weight loss from BW was similar between groups receiving higher vs lower AA doses (MD = 0.63; 95% CI, −0.48 to 1.75; *P* = 0.26) (Figure 2). Days to regain BW were similar between groups, whether receiving higher AA or lower AA doses (MD = −0.72; 95% CI, −1.59 to 0.14; *P* = 0.1) (Figure 3).

At 36 weeks' postmenstrual age or hospital discharge, measures of weight were similar between higher AA and lower AA doses based on both absolute weight in grams (MD = 34.29; 95% CI, −72.65 to 141.23; *P* = 0.53) (Figure 4) and weight-for-age standard deviation score (SDS) (MD = −0.03; 95% CI, −0.15 to 0.09; *P* = 0.59) (Figure 5). At that same cross-sectional measurement, length in centimeters (MD = 0.06; 95% CI, −0.60 to 0.71; *P* = 0.87) (Figure 6), length-for-age SDS (MD = −0.09; 95% CI, −0.29 to 0.11; *P* = 0.37) (Figure 7), head circumference in centimeters (MD = −0.04; 95% CI, −0.26 to 0.18; *P* = 0.72) (Figure 8), and head circumference–for-age SDS (MD = −0.05; 95% CI, −0.19 to 0.08; *P* = 0.44) (Figure 9) were similar between groups.

At 2 years, growth measures were also similar with higher AA or lower AA doses. Assessments included SDS for weight (MD = −0.11; 95% CI, −0.30 to 0.07; *P* = 0.23) (Figure 10), length (MD = −0.11; 95% CI, −0.30 to 0.08; *P* = 0.26) (Figure 11), or head circumference (MD = −0.14; 95% CI, −0.36 to 0.08; *P* = 0.21) (Figure 12).

Differences in methodology may contribute to these null findings. Some interventions included a sustained maximum dose, whereas other interventions included dose differences during PN initiation and advancement to goal doses (Table 4). Because some trials evaluated AA dose in conjunction with higher vs lower ILE doses,[17,20,23,25] they

TABLE 5 Clinical trial summary for question 3: In preterm infants, compared with lower doses of parenteral AA, are higher doses of parenteral AA associated with neurodevelopmental outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or number
Balakrishnan[10]	Start AA at 3–4 g/kg/day vs 1–2 g/kg/day; both groups advanced to 4 g/kg/day	GA 24–30 weeks and BW 400–1250 g High AA: *n* = 85 Low AA: *n* = 83	*BSID III at 24 m* CS < 70: *n* = 3; *n* = 3 MS < 70: *n* = 3; *n* = 4 LS < 70: *n* = 4; *n* = 3 CS < 85: *n* = 12; *n* = 9 MS < 85: *n* = 9; *n* = 10 LS < 85: *n* = 22; *n* = 24
Bellagamba[12,c]	Comparison of maximum AA 3.5 g/kg/day vs maximum 2.5 g/kg/day	BW 500–1249 g High dose: *n* = 82 Low dose: *n* = 82	*BSID III at 24 m* CS: 94 ± 13.9; 93.8 ± 12.9 MS: 101 ± 12.3; 101.8 ± 9.2
Blanco[13]	Start AA at 2 g/kg/day and maximum 4 g/kg/day vs starting AA 0.5 g/kg/day and maximum 3 g/kg/day in the first week	GA > 24 weeks and BW < 1000 g Higher dose: *n* = 16 with long-term follow-up Lower dose: *n* = 16 with long-term follow-up	*BSID II* MDI 6 m: 84 ± 14; 88 ± 5 MDI 12 m: 81 ± 9; 84 ± 14 MDI 18 m: 73 ± 15; 84 ± 11[b] MDI 24 m: 57 ± 11; 63 ± 11 PDI 6 m: 82 ± 15; 86 ± 13 PDI 12 m: 71 ± 14; 76 ± 12 PDI 18 m: 74 ± 14; 79 ± 12 PDI 24 m: 67 ± 15; 64 ± 12 Cerebral palsy: *n* = 3; *n* = 1
Bloomfield[14]	Additional AA 1 g/day for 5 days administered through umbilical arterial catheter vs 0.45% saline administered through umbilical arterial catheter; baseline AA dose in PN was not influenced by protocol *Note*: Different sites used varying ILE, and this was not part of the protocol	BW < 1000 g Higher dose: *n* = numbers specified by each measure Lower dose: *n* = numbers specified by each measure	*BSID III at 24 m* CS: 94.2 ± 15.7 (*n* = 159); 95.7 ± 14.4 (*n* = 162) MS: 94.7 ± 15.7 (*n* = 159); 95.9 ± 13.0 (*n* = 162) LS: 89.4 ± 17.1 (*n* = 159); 92.5 ± 16.5 (*n* = 162) Cerebral palsy: *n* = 1 of 161; *n* = 9 of 163
Morris[26]	Group 1: AA 4 g/kg/day; SO-ILE started at 2 g/kg/day advanced to 3.5 g/kg/day by day 3; dextrose started at ~5.5 mg/kg/min and advanced by ~1.5 mg/kg/min daily to goal 12–14 mg/kg/min Group 2: Start AA 3 g/kg/day and advanced to 4 g/kg/day by day 2; SO-ILE started 1 g/kg/day and advanced to 3.5 g/kg/day by day 4; dextrose start ~4 mg/kg/min and advanced by ~1.5 mg/kg/min daily to goal 12–14 mg/kg/min	GA <32 weeks and BW < 1500 g Group 1: *n* = 16 with long-term follow-up Group 2: *n* = 13 with long-term follow-up	*BSID III at 24 m* CS: 96.3 ± 14.9; 92.3 ± 22.8 MS: 88.1 ± 19.9; 89.2 ± 20.4 LS: 95.5 ± 18.2; 94.8 ± 22.1
Roelants[27]	Group 1: AA 2.4 g/kg/day; SO-ILE started on second day 1.4 g/kg/day then advanced to 2.8 g/kg/day Group 2: AA 2.4 g/kg/day; SO-ILE started immediately 2 g/kg/day advanced to 3 g/kg/day Group 3: AA 2.4 g/kg/day; SO,MCT,OO,FO-ILE started immediately at 2 g/kg/day and advanced to 3 g/kg/day Group 4: AA 3.6 g/kg/day; SO-ILE started immediately 2 g/kg/day and advanced to 3 g/kg/day	BW < 1500 g Group 1: *n* = 44 Group 2: *n* = 21 Group 3: *n* = 24 Group 4: *n* = 24 Group 5: *n* = 21	*BSID III at 24 m* CS < 70: *n* = 2; *n* = 0; *n* = 1; *n* = 1; *n* = 1 MS < 70: *n* = 2; *n* = 0; *n* = 1; *n* = 0; *n* = 1 Cerebral palsy: *n* = 1; *n* = 0; *n* = 1; *n* = 2; *n* = 3

(Continues)

TABLE 5 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD or number
	Group 5: AA 3.6 g/kg/day; SO,MCT,OO,FO-ILE started immediately at 2 g/kg/day and advanced to 3 g/kg/day		

Abbreviations: AA, amino acid; BSID III, Bayley Scales of Infant Development, 3rd edition; BW, birth weight; CS, cognitive scale; FO, fish oil; GA, gestational age at birth; ILE, lipid injectable emulsion; LS, language scale; m, months; MCT, medium-chain triglyceride; MDI, mental developmental index; MS, motor scale; OO, olive oil; PDI, psychomotor developmental index; SO, soybean oil.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

[c]Clinical trials also included enteral supplementation of protein.

could not be included in the combined analysis. These trials cannot be utilized to inform recommendations for this question, given that they examined multiple interventions simultaneously.

While multiple outcomes were significantly improved when trials were individually assessed for higher vs lower AA doses,[11,19,21,22,24] a single trial detected worse length-for-age SDS with higher AA.[10] The favorable outcomes were relevant to weight gain, as well as improvements in length and head circumference. Therefore, with these considerations and the low-quality evidence, the strong recommendation for parenteral AA dosing is based on the range tested in the studies included in the combined analyses.

Secondary outcomes

Combined analyses of secondary outcomes assessing effects of higher vs lower AA dose were possible for IVH, NEC, BPD, sepsis, ROP, blood urea nitrogen (BUN), length of stay, and mortality (Supporting Information: Table 7; Supporting Information: Figures 2–9). For sepsis, a funnel plot was created and a regression-based Egger test for small study effects was run to test for publication bias. There was no indication of publication bias ($Z = -0.08$, $P = 0.937$) (Supporting Information: Figure 10).

Two individual trials showed a significantly higher risk of sepsis with a higher dose of AA.[22,57] However, one of these trials altered both ILE dose and composition and could not be included in the combined analysis.[57] The single trial that evaluated a higher AA dose (initiation dose of 3.5 g/kg/day) detected a higher rate of sepsis in the group that received an initial dose of 3.5 g/kg/day.[22] A separate trial identified higher rates of sepsis in infants receiving an initial AA dose of 3.5 g/kg/day as compared with 2 g/kg/day. However, the two groups also differed in ILE composition, and, therefore an independent effect of the AA dose cannot be deciphered.[57] In the context of these findings, we advise initiating parenteral AA at a dose of no more than 3 g/kg/day and recommend evaluating sepsis as a primary outcome for future studies. In addition, one trial, comparing a maximum dose of 4 vs 2.5 g/kg/day, showed a lower incidence of hyperglycemia with a higher AA dose.[16] While a lower risk of hyperglycemia would be beneficial, this result is not consistently identified in studies. Taking into account other considerations such as concerns of impaired neurodevelopment with higher doses (as discussed in question 3), we do not advise a higher dose of AA for the purpose of lowering blood glucose levels.

In combined analysis, BUN was not significantly different between groups (MD = 1.23 mg/dl; 95% CI, −2.34 to 4.80; $P = 0.5$) (Supporting Information: Figure 9). However, of the studies that could not be included in the combined analysis due to measurement units and/or distribution measures, three individual trials did find significantly higher measures of urea metabolism with a higher AA dose (Supporting Information: Table 7).[14,18,25] The clinical relevance of these higher levels remains unclear.

Question 3: In preterm infants, compared with lower doses of parenteral AA, do higher doses of parenteral AA improve neurodevelopmental outcomes?

Recommendation: In considering the maximal target dose, we recommend providing parenteral AA doses at a minimum of 3 g/kg/day without increasing beyond 3.5 g/kg/day. The current evidence remains limited in distinguishing any benefit—namely, improved neurodevelopment—comparing a maximum AA dose of 3.5 vs 4 g/kg/day, and there is the suggestion that exceeding 3.5 g/kg/day may not be without harm.

Quality of evidence: Low

Strength of recommendation: Strong

Rationale for recommendation: Similar to question 2, initial AA doses and maximum target doses varied in the clinical trials assessed (Table 5). Initial doses were as low as 0.5–1 g/kg/day, and the maximum target dose range studied was 3–4 g/kg/day. One trial provided AA doses >4 g/kg/day based on the study protocol intending to provide an additional 1 g/day in the intervention group.[14] The single trial targeting up to 4.5 g/kg/day assessed in question 2 with increased risk for sepsis did not evaluate neurodevelopment. One trial evaluated AA dose and ILE dose and composition.[27] The BSID, 2nd and 3rd editions, represented the most common instrument utilized in trials. Mean values of BSID and dichotomous outcomes (ie, using cutoff scores below one or two standard deviations below the population mean) were utilized, as well as different versions of the BSID based on the era in which the study was completed (Table 5). One trial showed that higher AA doses were associated with lower scores at one measurement time, 18 months' corrected age, in a relatively small group of infants.[13] Scores at 2 years'

TABLE 6 Clinical trial summary for question 4: In preterm infants, compared with lower ILE doses, are higher ILE doses associated with growth outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD, median (25th–75th % or IQR), or *n*
Alburaki[28]	Starting SO-ILE higher (2 g/kg/day) vs lower (0.5 g/kg/day if ≤1000 g or 1 g/kg/day if >1000 g); final dose 3 g/kg/day for both groups	GA < 32 weeks and BW < 1500 g Higher dose: *n* = 45 Lower dose: *n* = 38	Days to regain BW: 10.5 (8–13); 11.5 (8–16) Maximum Wt loss, %: 10.4 ± 3.6; 12.7 ± 4.6[b] Wt at 36 weeks/dc, g: 2278 ± 303; 2165 ± 301 WASDS at 36 weeks/dc: −1.22 ± 0.71; −1.49 ± 0.74 Length at 36 weeks/dc, cm: 43.1 ± 2.4; 42.9 ± 3.1 LASDS at 36 weeks/dc: −1.76 ± 0.89; −1.86 ± 1.30 HC at 36 weeks/dc, cm: 31.3 ± 1.5; 30.5 ± 1.4 HCSDS at 36 weeks/dc: −1.09 ± 0.96; −1.59 ± 0.98[b] Weight <10th percentile at 36/40 weeks: *n* = 17; *n* = 25[b]
Can[17]	Start AA 3 g/kg/day with advance to 4 g/kg/day with ILE starting at 2 g/kg/day advanced to 3 g/kg/day by second day vs start AA 1.5 g/kg/day with advance to 4 g/kg/day with ILE starting at 1 g/kg/day advanced to 3 g/kg/day by fourth day	GA 27–33 weeks and AGA Earlier, higher AA and ILE doses: *n* = 25 Lower doses: *n* = 25	Days to regain BW: 12.7 ± 2.8; 14.2 ± 3.0 Wt at 40 weeks, g: 3180 ± 474; 2992 ± 445
Drenckpohl[29]	Compare SO-ILE starting at 2 g/kg/day vs starting at 0.5 g/kg/day; both groups advanced to 3 g/kg/day	GA 26–32 weeks and BW 750–1500 g and AGA Higher dose: *n* = 55 Lower: *n* = 55	Days to regain BW: 12.5 ± 3.68; 12.86 ± 3.76 Wt at 36 weeks/dc, g: 1894.27 ± 392.05; 1946.66 ± 771.1 Length at 36 weeks/dc, cm: 42.6 ± 3.02; 43.14 ± 4.35 HC at 36 weeks/dc, cm: 30.92 ± 2.20; 31.17 ± 2.49
Morgan[20]	Maximum dose of AA and ILE 3.8 g/kg/day and dextrose dose of 15.6 g/kg/day vs maximum dose of AA and ILE 2.8 g/kg/day and dextrose dose of 13.5 g/kg/day; both groups used SO-ILE	GA <29 weeks and BW < 1200 g Higher doses: *n* = 74 Lower doses: *n* = 76	Wt at 28 days, g: 1269 ± 222; 1212 ± 242 Wt at 36 weeks/dc, g: 2082 ± 293; 1976 ± 346 WASDS at 36 weeks/dc: −1.41 ± 0.72; −1.68 ± 0.88 ΔWt SDS birth to 28 days: −1.05 ± 0.71; −1.19 ± 0.75 ΔWt SDS birth to 36 weeks: −1.41 ± 0.72; −1.68 ± 0.88 HC at 28 days, cm: 27.1 ± 1.6; 26.5 ± 1.7 HC at 36 weeks/dc, cm: 31.6 ± 1.3; 31.1 ± 1.5[b] HCSDS at 36 weeks/dc: −0.93 ± 1.06; −1.32 ± 1.18[b] ΔHC first 28 days, cm/month: 3.1 ± 0.9; 2.6 ± 0.9[b] ΔHC SDS birth to 28 days: −1.51 ± 0.87; −1.81 ± 0.86 ΔHC SDS birth to 36 weeks: −0.93 ± 1.06; −1.32 ± 1.18[b]
Tagare[23]	Comparison of AA 3 g/kg with SO-ILE 2 g/kg vs starting AA 1 g/kg advanced to 2 g/kg with ILE starting on day 3 at 1 g/kg/day without dose increase	GA <37 weeks and BW < 1500 g Higher doses: *n* = 17 Lower doses: *n* = 17	Days to regain BW: 9.5 ± 6.7; 11.5 ± 6.7
Tan[25,c]	Comparison of effect from PN with 20% more energy using starting dose of AA and ILE at 1 g/kg/day; both advanced to 4 g/kg/day (117 kcal/kg/day) vs advancement to target dose of 3 g/kg/day for AA and ILE (93 kcal/kg/day)	GA <29 weeks Higher doses: *n* = 68 Lower doses: *n* = 74	Days to regain BW: 10.3 (6.3); 13.9 (6.3)[b] Wt at 36 weeks/dc, g: 2136 ± 345; 2090 ± 293 WASDS at 36 weeks/dc: −1.3 ± 0.9; −1.4 ± 0.8 Length at 36 weeks, cm: 42.9 ± 2.3; 42.4 ± 2LASDS at 36 weeks/dc: −2.3 ± 1.3; −2.6 ± 1HC at 36 weeks/dc, cm: 31.1 ± 1.5; 31.4 ± 1HCSDS at 36 weeks/dc: 1.0 ± 1.2; −0.8 ± 1.1
Vlaardingerbroek[25]	Comparison of effect of higher vs lower AA and early vs delayed ILE Group 1: Immediate start of AA 2.4 g/kg/day with ILE started	BW < 1500 g Group 1: *n* = 49 Group 2: *n* = 47 Group 3: *n* = 48	GV ×28 days, g/kg/day: 13.4 ± 4.7; 12.3 ± 5.8; 13.1 ± 5.7 GV through dc or 40 weeks, g/kg/day: 25.0 ± 5.2; 27.0 ± 7.3; 25.8 ± 8.1 ΔWASDS birth to DOL 28: −1.3 ± 1.0; −1.5 ± 1.1; −1.3 ± 1.1

(Continues)

TABLE 6 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD, median (25th–75th % or IQR), or *n*
	at 2 g/kg/day advanced to 3 g/kg/day Group 2: Immediate start of AA 3.6 g/kg/day with ILE started at 2 g/kg/day advanced to 3 g/kg/day Group 3: Immediate start of AA 2.4 g/kg/day; SO-ILE started on second day at 1.4 g/kg/day advanced to 2.8 g/kg/day *Note*: Infants in groups 1 and 2 exposed to ILE with SO,MCT,OO,FO-ILE or SO-ILE		ΔWASDS birth to 40 weeks' PMA or dc: −0.3 ± 1.2; −0.03 ± 1.3; −0.1 ± 1.4 HC velocity birth to 28 days, cm/week: 0.57 ± 0.29; 0.59 ± 0.24; 0.66 ± 0.37 HC velocity birth to dc, cm/week: 0.81 ± 0.15; 0.84 ± 0.13; 0.83 ± 0.13 ΔHCSDS birth to 28 days: −0.9 ± 0.9; −0.9 ± 0.9; −0.6 ± 1.2 ΔHCSDS birth to 40 weeks or dc: 0.2 ± 1.0; 0.6 ± 1.1; 0.5 ± 1.0

Abbreviations: AA, amino acid; BW birth weight; dc, discharge; DOL, day of life; FO fish oil; GA, gestational age at birth; GV growth velocity; HC, head circumference; HCSDS, head circumference–for-age standard deviation score; ILE, lipid injectable emulsion; LASDS, length-for-age standard deviation score; MCT, medium-chain triglyceride; OO, olive oil; PMA, postmenstrual age; SDS, standard deviation score; SO, soybean oil; WASDS weight-for-age standard deviation score; Wt, weight.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

[c]Clinical trials also included enteral supplementation of protein.

corrected age were not different between the groups. Also notable in this study, scores at 2 years' corrected age were considerably low in both groups.[13] Due to heterogeneity in evaluations of neurodevelopment, both in the testing instrument and testing age, as well as a single study where AAs were not the only nutrients affected by randomization,[26] combined evaluation of BSID scores for this question was not possible. A combined analysis was possible for the outcome cerebral palsy. Although the risk difference (RD) did not meet statistical significance (RD = 0.05; 95% CI −0.00 to 0.10; $P = 0.06$), the directional consistency between study outcomes in favor of lower AA warrants caution (Figure 13). In the trials included in combined analysis, the higher target doses were 3.6 g/kg/day,[27] 4 g/kg/day,[13] and an additional 1 g/day above routine AA dose.[14] The strong recommendation for parenteral AA dosing between 3 and 3.5 g/kg/day is within the range tested in the individual studies and reflects caution from the clinical panel until future studies using higher AA are run to clarify the issue.

Question 4: In preterm infants, compared with lower ILE doses, do higher ILE doses improve growth outcomes?

Recommendation: To improve growth, we recommend daily advancement of ILE to a dose of 3 g/kg/day if using SO-ILE or multicomponent ILE. We strongly emphasize the need for attention to ILE composition when making decisions on ILE dose to ensure the provision of sufficient fatty acids for the purposes of preventing an essential fatty acid deficiency (EFAD). Providing suboptimal ILE doses that are associated with a risk for an EFAD may impair growth and increase the risk for other adverse outcomes.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: Study design heterogeneity prevented combined analysis for this question. Studies compared lower vs higher starting ILE doses with the same maximum dose.[28,29] The lowest starting dose was 0.5 g/kg/day, and commonly, the higher starting dose was 2 g/kg/day. In contrast, other studies compared lower vs higher ILE maximum doses; the highest maximum dose was 3.8 g/kg/day (Table 6).[23–25] Most studies also included an intervention that altered parenteral AA and/or dextrose dose in addition to ILE dose.[17,20,23–25] For those studies, effects specifically attributable to the ILE were unable to be separated out for a combined analysis. All studies utilized ILE with the same composition between study groups. A higher starting ILE dose in a single study was associated with a smaller postnatal weight loss between groups.[28] However, the clinical implications of that single measurement are unclear. A weight near the time of discharge was similar between groups, yet fewer infants in the higher-dose group had a weight in the <10th percentile for age at discharge, suggesting a benefit to a higher starting dose. Based on the SDS, head size was greater with the higher dose compared with the lower dose.[28]

A fundamental goal for providing ILE is EFAD prevention.[58] Specific dose reductions of any ILE may lead to EFAD in preterm infants.[59,60] Hence, the strong recommendation accounts for the very low-quality evidence in conjunction with an awareness of risks of an EFAD. Also, we recommend caution and close attention to ensure the provision of sufficient fatty acids to prevent an EFAD if ever considering an ILE dose reduction. It is important to remember that the risk of an EFAD depends on the ILE's oil source(s) and dose.

Question 5: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, does altering the ILE composition by reducing the proportion of SO improve growth outcomes?

TABLE 7 Clinical trial summary for question 5: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, is altering the ILE composition by reducing the proportion of SO associated with growth outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD; median (25th–75th %)
Costa[30]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, starting 1.5 g/kg/day, advanced daily by 0.5–3 g/kg/day for both groups	BW ≤ 1250 g SO,MCT,OO,FO-ILE: *n* = 64 SO-ILE: *n* = 64	ΔWASDS birth to 36 weeks/dc: −0.94 ± 0.83 (*n* = 51); −1.07 ± 0.65 (*n* = 50) ΔLSDS birth to 36 weeks/dc: −1.06 ± 0.96 (*n* = 51); −1.51 ± 0.9 (*n* = 50)[b] ΔHCSDS birth to 36 weeks/dc: −0.65 ± 0.87 (*n* = 51); −1.07 ± 1.08 (*n* = 50)[b]
Gallini[31]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, starting 1.5 g/kg/day, advanced daily by 0.5–3 g/kg/day for both groups	GA ≤30 weeks and/or BW ≤ 1250 g SO,MCT,OO,FO-ILE: *n* = 47 SO-ILE: *n* = 46	WASDS at 24 months: −1.61 ± 1.43; −1.18 ± 1.32 LSDS at 24 months: −0.65 ± 1.18; −0.36 ± 0.97 HCSDS at 24 months: −0.59 ± 1.24; −0.45 ± 1.16
Repa[32]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, starting 1 g/kg/day, advanced to 3 g/kg/day for both groups	BW < 1000 g SO,MCT,OO,FO-ILE: *n* = 110 SO-ILE: *n* = 113	Wt at 36 weeks/dc, g: 2594 (2124–3029); 2479 (2175–2956) Length at 36 weeks/dc, cm: 45 (42.5–47); 44 (41.5–47) HC at 36 weeks/dc, cm: 32 (30.6–33.5); 32 (30.7–33.1)
Savini[33]	Comparison of 5 different ILEs: SO,MCT-ILE vs SO,MCT,FO-ILE vs SO,OO-ILE vs SO,MCT,OO,FO-ILE vs SO-ILE Starting dose 1 g/kg/day, advanced to 3 g/kg/day by 0.5 g/kg/day for all groups	BW 500–1249 g SO,MCT-ILE: *n* = 30 SO,MCT,FO-ILE: *n* = 27 SO,OO-ILE: *n* = 29 SO,MCT,OO,FO-ILE: *n* = 28 SO-ILE: *n* = 30	Days to regain BW: 12 ± 5; 10 ± 5; 14 ± 9; 12 ± 5; 11 ± 5 Maximum wt loss, %: 12 ± 6; 11 ± 5; 14 ± 5; 15 ± 6; 11 ± 6
Skouroliakou[34]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE; maximum 3 g/kg/day in both groups	GA < 32 weeks and BW < 1500 g SO,MCT,OO,FO-ILE: *n* = 14 SO-ILE: *n* = 18	Wt at 36 weeks/dc, g: 1780 ± 460; 2010 ± 360 Length at 36 weeks/dc, cm: 45.96 ± 3.2; 46.8 ± 3.05 HC at 36 weeks/dc, cm: 31.52 ± 1.71; 31.85 ± 1.67
Thanhaeuser[35]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE; maximum 3 g/kg/day in both groups	BW < 1000 g SO,MCT,OO,FO-ILE: *n* = 86 assessed at 12 months; *n* = 81 assessed at 24 months SO-ILE: *n* = 88 assessed at 12 months; *n* = 83 assessed at 24 months	Wt at 12 months, kg: 8.9 (8–10); 8.95 (8.1–9.9) WASDS at 12 months: −0.57 (−1.5 to 0.4); −0.44 (−1.39 to 0.41) Length at 12 months, cm: 74 (72–76); 74 (71.63–76) LASDS at 12 months: −0.59 (−1.25 to 0.38); −0.5 (−1.25 to 0.28) HC at 12 months, cm: 45 (43.9–46); 45 (43.7–46.3) HCSDS at 12 months: −1.2 (−2.06 to 0.01); −1.1 (−2.3 to 0.5) Wt at 24 months, kg: 11.4 (10.2–12.9); 11.6 (10.2–12.9) WASDS at 24 months: −0.22 (−1.09 to 0.68); −0.2 (−1.21 to 0.57) Length at 24 months, cm: 85 (82–88); 85 (83–88) LASDS at 24 months: −0.59 (−1.4 to 0.23); −0.59 (−1.29 to 0.22) HC at 24 months, cm: 47 (46–48.5); 47 (46–48) HCSDS at 24 months: −0.95 (−1.82 to 0.07); −0.98 (−2.49 to 0.33)
Vlaardingerbroek[36]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, both groups starting 2 g/kg/day	BW < 1500 g SO,MCT,OO,FO-ILE: *n* = 48 SO-ILE: *n* = 48	Days to regain birth Wt: 8 (3–11); 8 (6–12) GV × 28 days, g/kg/day: 13.8 ± 5.6; 11.9 ± 4.9 GV through dc or 40 weeks, g/kg/day: 27.6 ± 6.5; 24.5 ± 6.0

(Continues)

TABLE 7 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SD; median (25th–75th %)
	advanced to 3 g/kg/day		ΔWASDS birth to DOL 28: −1.2 ± 1.1; −1.6 ± 1.0 ΔWASDS birth to 36 weeks PMA or dc: 0.2 ± 1.1; −0.5 ± 1.3 HC velocity birth to 28 days, cm/week: 0.58 ± 0.27; 0.58 ± 0.26 HC velocity birth to dc, cm/week: 0.85 ± 0.14; 0.80 ± 0.14 ΔHCSDS birth to 28 days: −0.9 ± 0.9; −0.9 ± 0.9 ΔHCSDS birth to 36 weeks or dc: 0.7 ± 0.9; 0.1 ± 1.1
Wang[37]	Comparison of three different ILEs Group 1: SO, OO-ILE Group 2: SO, MCT-ILE Group 3: SO-ILE, all started at 1 g/kg/day advanced to 3 g/kg/day	GA < 37 weeks and BW < 2000 g Group 1: *n* = 50 Group 2: *n* = 50 Group 3: *n* = 50	Days to regain BW: Group 1: 11.13 ± 5.6 Group 2: 12.52 ± 6.29 Group 3: 12.30 ± 5.23

Abbreviations: AA, amino acids; BW, birth weight; FO fish oil; GA, gestational age at birth; GV growth velocity; HC, head circumference; HCSDS, head circumference–for-age standard deviation score; ILE, lipid injectable emulsion; LASDS, length-for-age standard deviation score; LSDS, length standard deviation score; MCT, medium-chain triglyceride; OO, olive oil; SO, soybean oil; WASDS, weight-for-age standard deviation score; Wt, weight.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

TABLE 8 Clinical trial summary for question 6: In preterm infants, compared with a higher dose of macronutrients (AA, dextrose, ILE), is a lower dose of macronutrients associated with PNALD?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] *n* or %
Alburaki[28]	Starting higher dose of SO-ILE (2 g/kg/day) vs lower dose (0.5 g/kg/day if ≤1000 g or 1 g/kg/day if >1000 g); final dose 3 g/kg/day for both groups	GA < 32 weeks and BW < 1500 g Higher dose: *n* = 45 Lower dose: *n* = 38	PNALD: *n* = 4; *n* = 0
D'Ascenzo[38]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE as well as ILE dose: Group 1: SO,MCT,OO,FO-ILE at 2.5 g/kg/day Group 2: SO-ILE at 2.5 g/kg/day Group 3: SO,MCT,OO,FO-ILE at 3.5 g/kg/day Group 4: SO-ILE at 3.5 g/kg/day	BW 500–1249 g Group 1: *n* = 21 Group 2: *n* = 22 Group 3: *n* = 18 Group 4: *n* = 19	PNALD: *n* = 1; *n* = 1; *n* = 0; *n* = 3
Levit[39]	SaO+SO or SO-ILE with maximum 1 g/kg/day vs maximum 3 g/kg/day	GA ≤ 29 weeks Low dose: *n* = 69 High dose: *n* = 67	PNALD: 8%; 11%
Li[19]	Starting AA 1.8–2.5 g/kg/day advanced to 4–4.5 g/kg/day vs starting AA 1–1.5 g/kg/day advanced to 3.5 g/kg/day	GA <37 weeks and BW < 2500 g Higher AA: *n* = 110 Lower AA: *n* = 81	PNALD: *n* = 3; *n* = 5
Morgan[20]	Maximum AA and ILE 3.8 g/kg/day and dextrose 15.6 g/kg/day vs maximum AA and ILE 2.8 g/kg/day and dextrose 13.5 g/kg/day; both groups used SO-ILE	GA <29 weeks and BW < 1200 g Higher doses: *n* = 74 Lower doses: *n* = 76	PNALD: *n* = 6; *n* = 8

Abbreviations: AA, amino acid; BW, birth weight; FO, fish oil; GA, gestational age at birth; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; PNALD, parenteral nutrition–associated liver disease; SaO, safflower oil; SO, soybean oil.

[a]Results are reported in respective order of groups named in participant column.

TABLE 9 Clinical trial summary for questions 7a and 7b.

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome,[a] *n*
Studies in which comparisons included ILE that did not contain FO			
Gobel[40]	Compare SO,OO-ILE vs SO-ILE, starting 0.5 g/kg/day advanced to 3 g/kg/day for both groups	GA 28–36 weeks SO,OO-ILE: *n* = 24 SO-ILE: *n* = 21	PNALD: *n* = 0; *n* = 0
Wang[41]	Compare SO,OO-ILE vs SO-ILE, starting 1 g/kg/day advanced to 3 g/kg/day for both groups	GA < 37 weeks and BW < 2000g SO,OO-ILE: *n* = 50 SO-ILE: *n* = 50	PNALD: *n* = 2; *n* = 2
Studies in which comparisons included ILE that contained FO			
Costa[30]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, starting 1.5 g/kg/day advanced daily by 0.5–3 g/kg/day for both groups	BW ≤ 1250 g SO,MCT,OO,FO-ILE: *n* = 64 SO-ILE: *n* = 64	PNALD: *n* = 5; *n* = 12
D'Ascenzo[38]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE as well as ILE dose Group 1: SO,MCT,OO,FO-ILE at 2.5 g/kg/day Group 2: SO-ILE at 2.5 g/kg/day Group 3: SO,MCT,OO,FO-ILE at 3.5 g/kg/day Group 4: SO-ILE at 3.5 g/kg/day	BW 500–1249 g Group 1: *n* = 21 Group 2: *n* = 22 Group 3: *n* = 18 Group 4: *n* = 19	PNALD: *n* = 1; *n* = 1; *n* = 0; *n* = 3
Repa[32]	Comparison of SO,MCT,OO,FO-ILE vs SO-ILE, starting 1 g/kg/day advanced to 3 g/kg/day for both groups	BW < 1000 g SO,MCT,OO,FO-ILE: *n* = 110 SO-ILE: *n* = 113	PNALD: *n* = 11; *n* = 18
Savini[33]	SO,MCT-ILE vs SO,MCT,FO-ILE vs SO,OO-ILE vs SO,MCT,OO,FO-ILE vs SO-ILE Starting 1 g/kg/day advanced to 3 g/kg/day by 0.5 g/kg/day for all groups	BW 500–1249 g SO,MCT-ILE: *n* = 30 SO,MCT,FO-ILE: *n* = 27 SO,OO-ILE: *n* = 29 SO,MCT,OO,FO-ILE: *n* = 28 SO-ILE: *n* = 30	PNALD: *n* = 1; *n* = 1; *n* = 0; *n* = 1; *n* = 0

Note: *Question 7a*: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, is a reduction in SO *using any multicomponent-oil ILE* associated with PNALD? *Question 7b*: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, is a reduction in SO *using only multicomponent-oil ILE that include FO* associated with PNALD?

Abbreviations: BW, birth weight; FO, fish oil; GA, gestational age at birth; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; PNALD, parenteral nutrition–associated liver disease; SO, soybean oil.

[a]Results are reported in respective order of groups named in participant column.

TABLE 10 Clinical trial summary for question 9: In preterm infants, is a reduced dose of ILE associated with the risk of sepsis?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome,[a] %
Levit[39]	SaO+SO or SO-ILE with maximum 1 g/kg/day vs maximum 3 g/kg/day	GA ≤ 29 weeks Low dose: *n* = 69 High dose: *n* = 67	Sepsis: 9%; 4%
Morgan[20]	Maximum AA and ILE 3.8 g/kg/day and dextrose of 15.6 g/kg/day vs maximum AA and ILE 2.8 g/kg/day and dextrose 13.5 g/kg/day; both groups used SO-ILE	GA <29 weeks and BW < 1200 g Higher doses: *n* = 74 Lower doses: *n* = 76	Sepsis: *n* = 26; *n* = 28 *Note*: This was measured in survivors at 36 weeks' corrected age.

Abbreviations: AA, amino acid; BW birth weight; GA, gestational age at birth; ILE, lipid injectable emulsion; SaO, safflower oil; SO, soybean oil.

[a]Results are reported in respective order of groups named in participant column.

Recommendation: At this time, we do not recommend any specific ILE composition for enhanced growth, given there was no evidence of benefit from any particular ILE.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: The method of reducing SO differed between studies. Some studies compared a multicomponent-oil ILE that included FO, while other studies included multicomponent-oil ILEs that included either olive oil or a medium-chain triglyceride–containing oil without FO.[37] As planned by the methodology for this guideline, all

TABLE 11 Clinical trial summary for question 10: In preterm infants, is the provision of parenteral micronutrients associated with growth outcomes and the risk for specific morbidities (eg, osteopenia of prematurity, BPD, or sepsis)?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Number, median (IQR or 25th–75th %), mean ± SD, %
Acetate			
Ali[42]	Comparison of PN with sodium provision as sodium acetate vs sodium chloride	GA < 33 weeks and BW < 1301 g Acetate: *n* = 27 Chloride: *n* = 26	IVH: *n* = 2; *n* = 8 NEC: *n* = 1; *n* = 4 Mortality: *n* = 2, *n* = 3 LOS: 50 (23); 54 (25)
Carnitine			
Crill[43]	PN with carnitine supplementation vs PN with no carnitine L-carnitine concentration was 130 mg/L, a formulation that would provide 20 mg/kg/day for a fluid rate of 150 ml/kg/day	GA ≤ 32 weeks and BW ≤ 1500 g With carnitine: *n* = 16 No carnitine: *n* = 13	Sepsis: *n* = 8; *n* = 7 Days to regain BW: 11.8 ± 6; 16.9 ± 6.3[b]
O'Donnell[44]	Carnitine added to PN at 30 mg/kg/day vs no carnitine in PN *Note*: carnitine added to enteral nutrition in both groups	GA < 32 weeks and BW < 1500 g Carnitine: *n* = 21 No carnitine: *n* = 20	NEC: *n* = 2; *n* = 4 BPD: *n* = 9; *n* = 6 LOS, days: 75 ± 28; 81 ± 37 Wt at 36 weeks/dc, g: 2264 ± 517; 2294 ± 546
Ozturk[45]	Carnitine added to PN at 30 mg/kg/day divided into three times per day IV when receiving PN, also provided via enteral route until age 7 days vs no carnitine	GA 28–38 weeks Carnitine: *n* = 30 No carnitine: *n* = 31	BPD: *n* = 2; *n* = 4
Pande[46]	PN with L-carnitine 50 µmol/kg/day vs PN without L-carnitine	GA <29 weeks Carnitine: *n* = 32 No carnitine: *n* = 31	IVH: *n* = 9; *n* = 6 BPD: *n* = 16; *n* = 12 ROP: 19%; 14% LOS: 69 (21–151); 56 (39–144) HyperTG: *n* = 0; *n* = 0 Wt at 36 weeks/dc, g: 2032 ± 416; 1972 ± 397 Length at 36 weeks/dc, cm: 43.0 ± 2.8; 42.6 ± 2.0 HC at 36 weeks/dc, cm: 30.8 ± 2.3; 30.3 ± 1.6 Days to regain BW: 11 (2–22); 11 (6–19)
Glutamine			
Poindexter[47]	PN with 20% glutamine vs PN without glutamine *Note*: AA solutions were isonitrogenous	BW 401–1000 g Glutamine: *n* = 721 No glutamine: *n* = 712	Sepsis: *n* = 301; *n* = 273 Mortality: *n* = 124; *n* = 127 LOS, days: 89 (49–184); 90 (54–159)
Wang[48]	Comparison of AA 1.7 g/kg/day + glutamine 0.3 g/kg/day vs AA 2 g/kg/day without supplemental glutamine	GA < 31 weeks Glutamine, *n* = 13 No glutamine, *n* = 13	NICU LOS, days: 42.5 ± 15.5; 41.2 ± 16 HC velocity birth to dc, cm/week: 0.58 ± 0.23; 0.74 ± 0.45
Manganese			
Fok[49]	Manganese administered in PN, 1 vs 0.0182 µmol/kg/day	All GA Higher Mn: *n* = 121 Lower Mn: *n* = 123	IVH: *n* = 7; *n* = 11 BPD: *n* = 25; *n* = 32 Sepsis: *n* = 27; *n* = 29 ROP: *n* = 3; *n* = 5 Mortality: *n* = 12; *n* = 17
Iron and/or erythropoietin			
Haiden[50]	Comparison of combined therapy of EPO, iron, vitamin B_{12} and folate vs EPO with iron	GA ≤ 32 weeks and BW 801–1300 g With vitamin B_{12}/folate: *n* = 31	IVH: *n* = 0; *n* = 2 ROP: *n* = 1; *n* = 0 Mortality: *n* = 3; *n* = 4 LOS: 97 (59–162); 89 (77–157)

TABLE 11 (Continued)

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Number, median (IQR or 25th–75th %), mean ± SD, %
		EPO/Fe alone: *n* = 33	
Haiden[51]	PN micronutrients (EPO 300 U/kg/day; iron dextran 1.5 mg/kg/day; vitamin B_{12} 3 mcg/kg/day) followed by enteral supplementation of nutrients including vitamin E vs no parenteral therapy/no EPO/only enteral provision of iron, folic acid, and vitamin E	GA ≤ 32 weeks and BW 450–800 g Parenteral intervention: *n* = 21 No parenteral intervention: *n* = 19	IVH: *n* = 0; *n* = 0 Mortality: *n* = 3; *n* = 2 LOS, days: 66 (44–170); 68 (52–213) Wt at 36 weeks/dc, g: 2075 (1400–3335); 2203 (1170–4815)
Qiao[52]	PN with iron 200 mcg/kg/day + EPO 400 U/kg twice per week vs PN with iron 200 µg/kg/day without EPO vs PN without iron or EPO	GA 28–34 weeks Iron+EPO: *n* = 30 Iron: *n* = 31 No iron or EPO: *n* = 30	Mortality: *n* = 2; *n* = 2; *n* = 1

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; dc, discharge; EPO, erythropoietin; GA, gestational age; HC, head circumference; HyperTG, hypertriglyceridemia; IV, intravenous; IVH, intraventricular hemorrhage; LOS, length of stay; NEC, necrotizing enterocolitis; NICU, neonatal intensive care unit; PN, parenteral nutrition; ROP, retinopathy of prematurity; Wt, weight.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

TABLE 12 Clinical trial summary for question 12: In preterm infants, is the use of insulin associated with improved growth outcomes?

Reference	Study design	GA and/or BW eligibility and participants (*n*)	Results/outcome[a] Mean ± SEM (*n*)
Alsweiler[53]	Insulin titration to achieve blood glucose concentrations 4–6 vs 8–10 mmol/L	GA < 30 weeks or BW < 1500 g and hyperglycemia develops Target 4–6 mmol/L: *n* = 43 Target 8–10 mmol/L: *n* = 45	Wt at 36 weeks/dc, g: 2196 ± 65 (*n* = 38); 2265 ± 59 (*n* = 43) WASDS 36 weeks/dc: −1.4 ± 0.16 (*n* = 38); −1.22 ± 0.15 (*n* = 43) Length at 36 weeks/dc, cm: 42.8 ± 0.4 (*n* = 38); 43.3 ± 0.4 (*n* = 43) LASDS at 36 weeks/dc: −2.07 ± 0.17 (*n* = 38); −1.91 ± 0.14 (*n* = 43) HC at 36 weeks/dc, cm: 30.7 ± 0.3 (*n* = 38); 30.9 ± 0.2 (*n* = 43) HCSDS at 36 weeks/dc: −1.7 ± 0.2 (*n* = 38); −1.6 ± 0.15 (*n* = 43) ΔWASDS birth to 36 weeks/dc: −1.08 ± 0.12 (*n* = 38); −1.34 ± 0.16 (*n* = 43) ΔLASDS birth to 36 weeks/dc: −1.68 ± 0.13 (*n* = 38); −1.82 ± 0.13 (*n* = 43) ΔHCSDS birth to 36 weeks/dc: −1.4 ± 0.22 (*n* = 38); −1.9 ± 0.14 (*n* = 43)[b]

Abbreviations: BW, birth weight; dc, discharge; GA, gestational age at birth; HC, head circumference; HCSDS, head circumference–for-age standard deviation score; LASDS, length-for-age standard deviation score; WASDS, weight-for-age standard deviation score; Wt, weight.

[a]Results are reported in respective order of groups named in participant column.

[b]Statistical significance between groups in primary study.

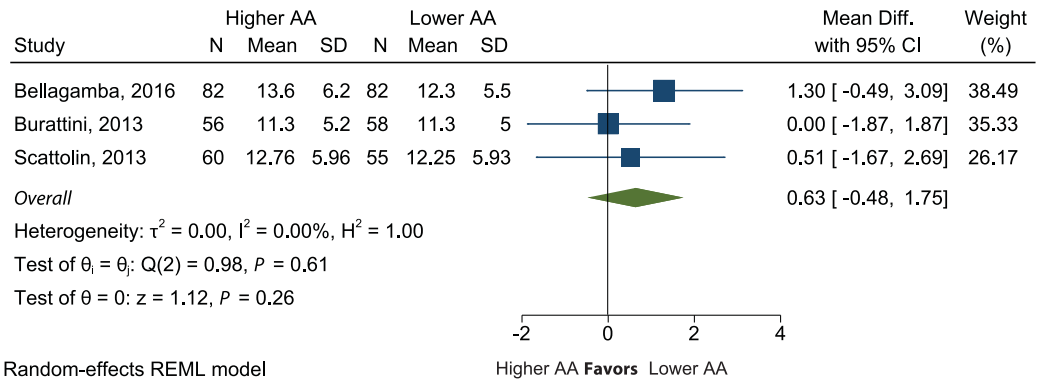

FIGURE 2 Mean difference in maximum percent weight loss in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

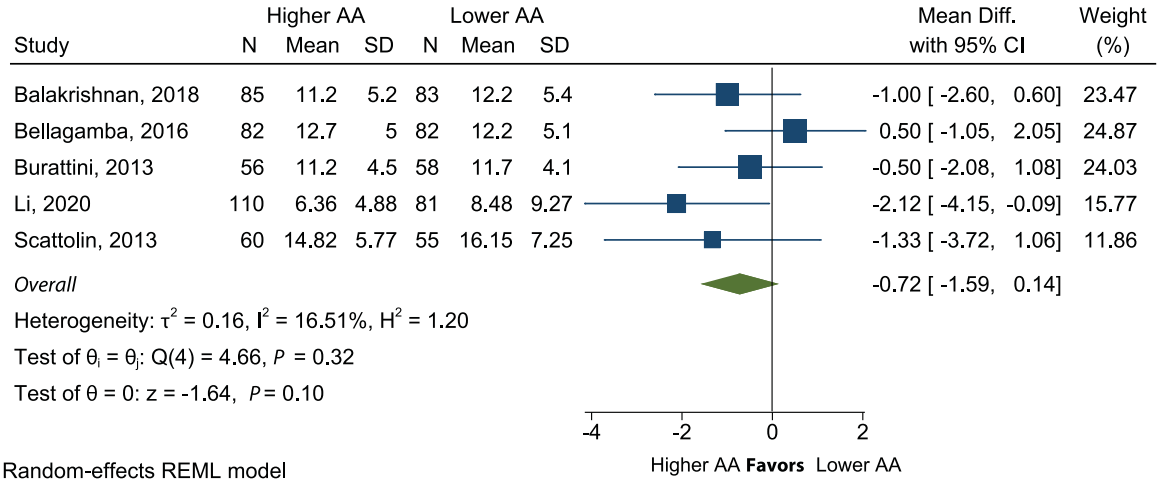

FIGURE 3 Mean difference in days to regain birthweight in patients with higher vs lower amino acid dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

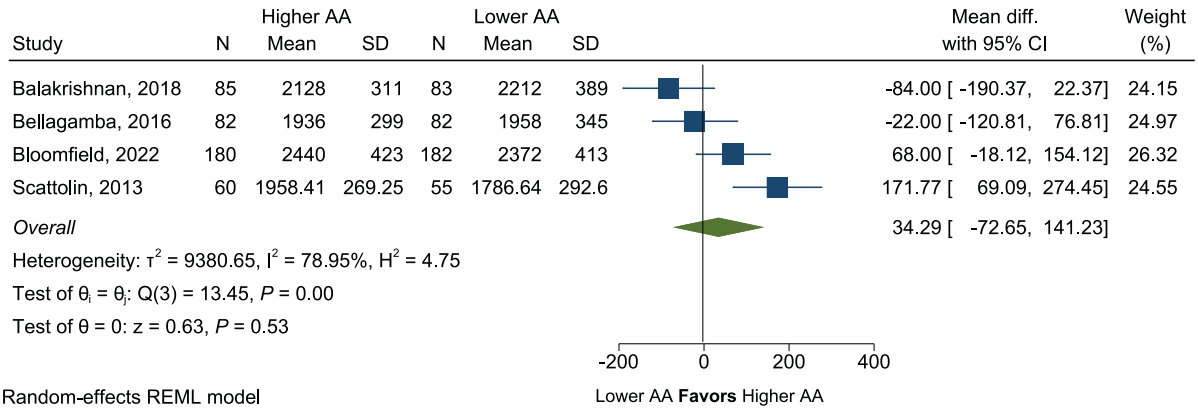

FIGURE 4 Mean difference in weight (grams) at 36 weeks' corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

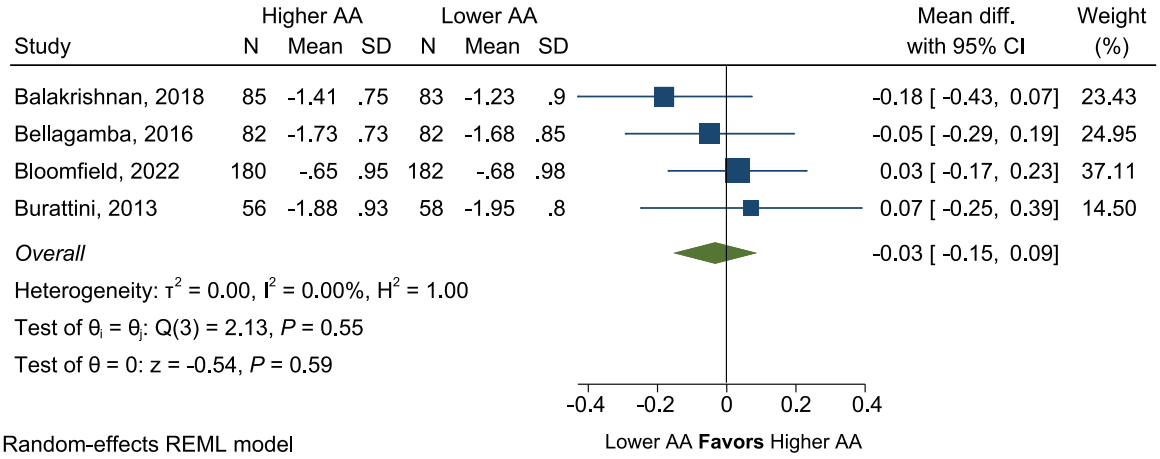

FIGURE 5 Mean difference in weight standard deviation score at 36 weeks' corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

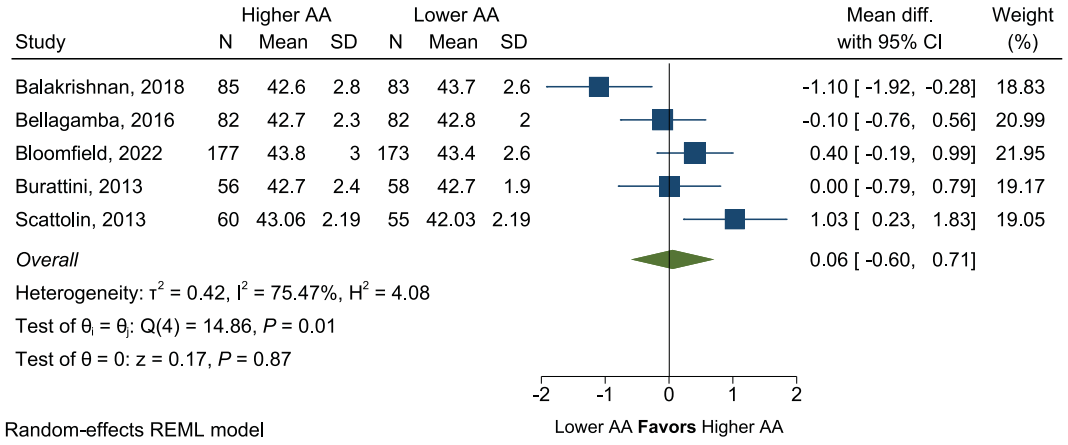

FIGURE 6 Mean difference in length (cm) at 36 weeks' corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

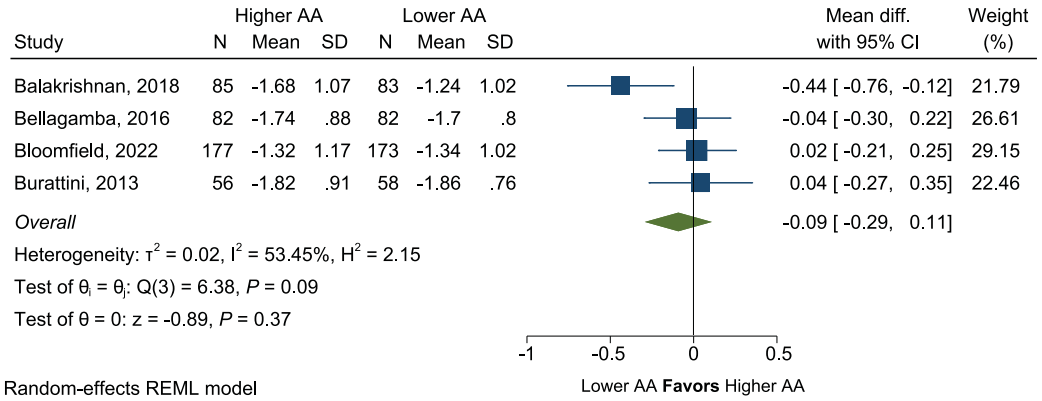

FIGURE 7 Mean difference in length standard deviation score at 36 weeks' corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

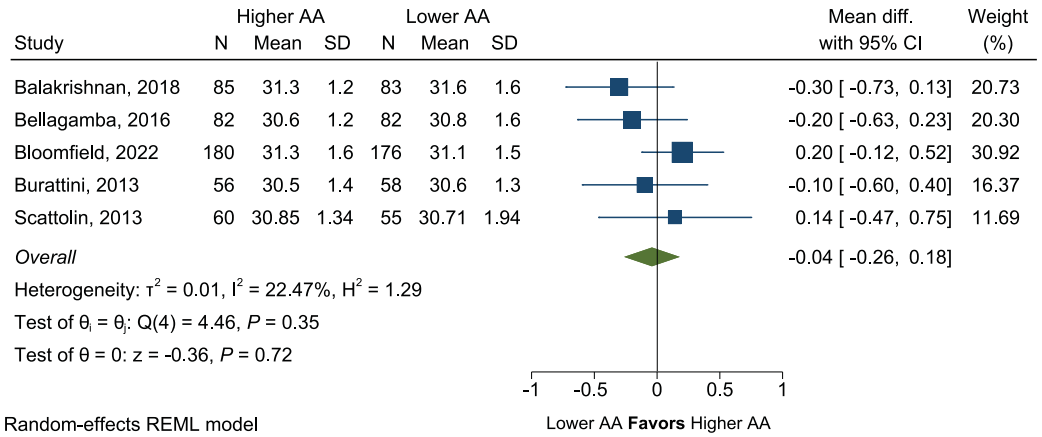

FIGURE 8 Mean difference in head circumference (cm) at 36 weeks' corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

ILE interventions were compared with SO-ILE in these studies. Heterogeneity in the growth measures, the times at which they were assessed, and the reported measures of central tendency prohibited a combined analysis (Table 7).

Two trials had multiple intervention groups.[33,37] Theoretically, groups could be combined in a manner that allowed for the appropriate comparison of a multicomponent-oil ILE to SO-ILE. Trials with multiple intervention groups could only be incorporated into the

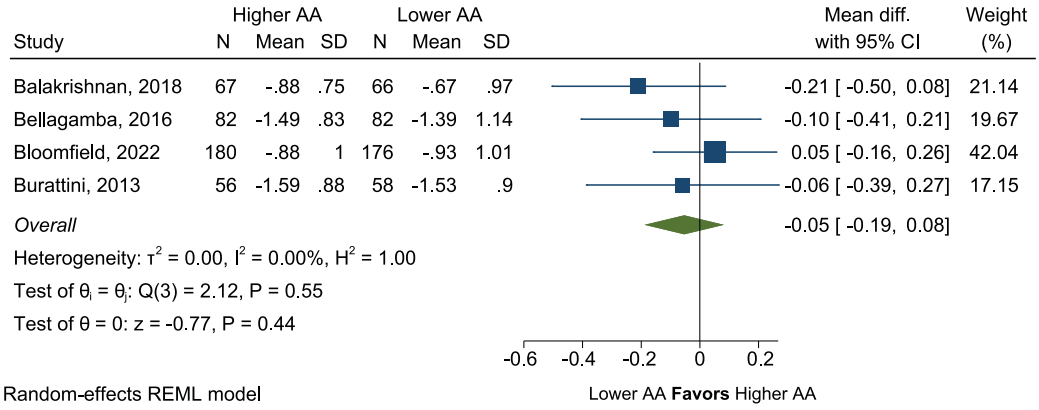

FIGURE 9 Mean difference in head circumference standard deviation score at 36 weeks corrected age or discharge in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

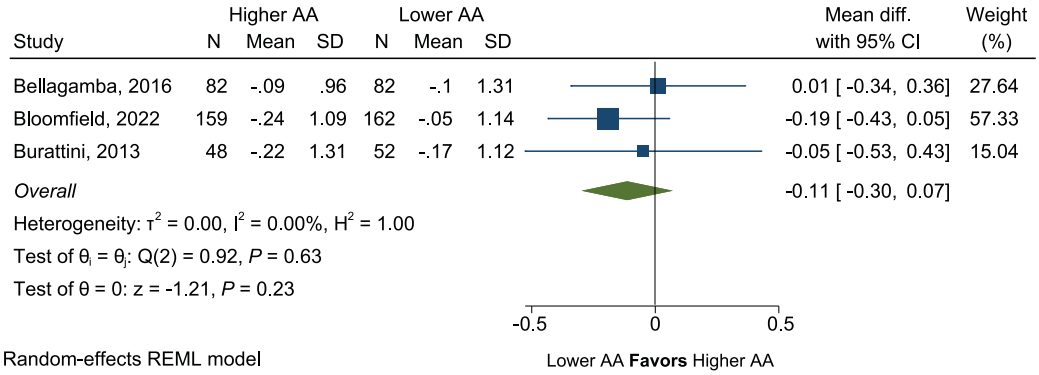

FIGURE 10 Mean difference in weight standard deviation score at 2 years in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

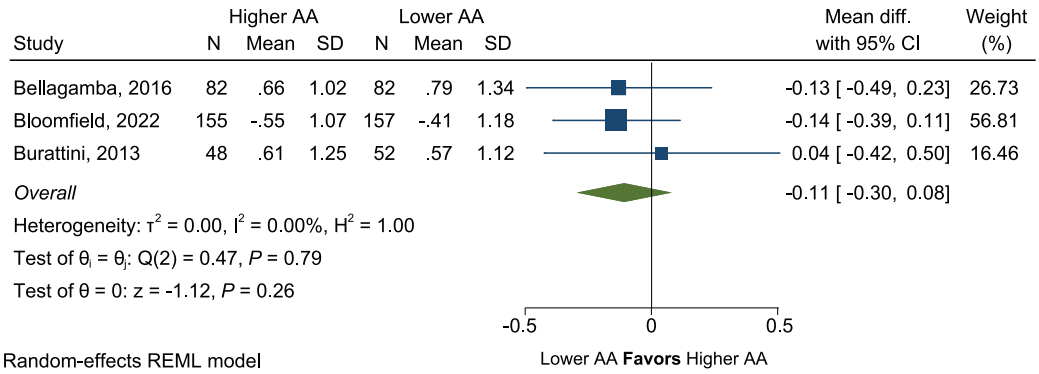

FIGURE 11 Mean difference in length standard deviation score at 2 years in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

analysis if counting control groups (treated with SO-ILE) twice in the analysis could be avoided. As such, in one of the studies,[37] an arbitrary decision would need to be made to exclude one of the study arms. Ultimately, given the few studies eligible for comparison, this would still leave insufficient numbers for a combined analysis. Thus, a combined analysis was not possible.

Collectively, at least one measure of all three parameters of weight gain and linear and head growth was evaluated in the individual trials. A single trial showed significantly smaller declines in SDS for length and head circumference from birth to 36 weeks' postmenstrual age or discharge in infants receiving a multicomponent-oil ILE with FO.[30] Otherwise, for all other

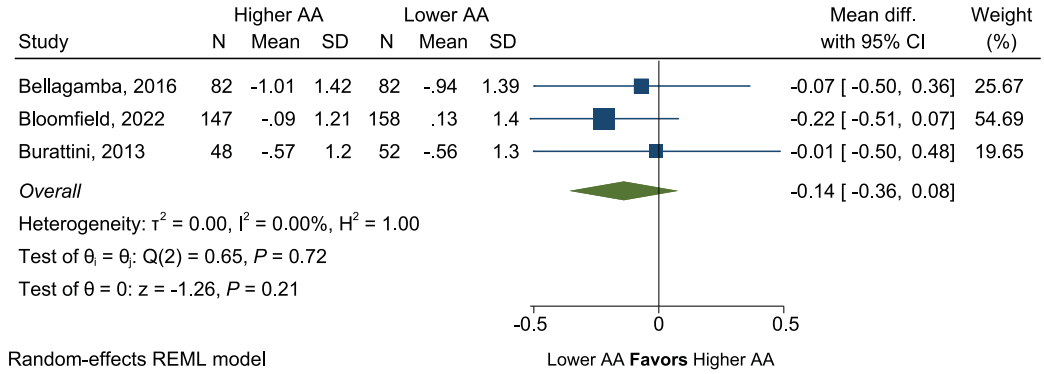

FIGURE 12 Mean difference in head circumference standard deviation score at 2 years in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; REML, restricted maximum likelihood.

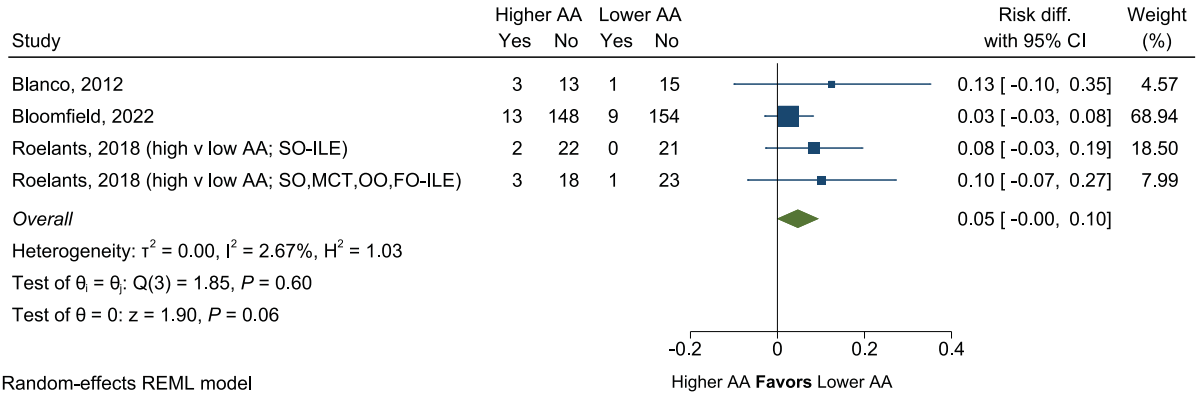

FIGURE 13 Risk difference in cerebral palsy in patients with higher vs lower AA dose. AA, amino acid; Diff., difference; FO, fish oil; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; REML, restricted maximum likelihood; SO, soybean oil.

individual studies, anthropometric outcomes measured relatively early (eg, days to regain BW) and later (eg, near discharge and postdischarge through 24 months) were not significantly different between groups. Hence, the available very low-quality evidence suggests no specific benefit of any ILE composition for growth outcomes.

Question 6: In preterm infants, compared with a higher dose of parenteral macronutrients (AA, dextrose, ILE), does a lower dose of macronutrients reduce the incidence of PNALD?

Recommendation: We do not recommend routinely reducing the dose of AA, dextrose, or ILE when providing PN to preterm infants for the purposes of preventing PNALD.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: We evaluated any trial able to address the question of dose of AA, dextrose, or ILE and PNALD risk. Considerable heterogeneity across the five study interventions imposed limits on compiling data (Table 8). Interventions included randomization of AA dose,[19] ILE dose and composition,[38] AA and ILE dose using the same ILE (SO-ILE),[20] and dose variation of the same ILE (Table 8).[28,39] No significant differences were identified in these individual trials. No studies isolated the effects of dextrose dose on PNALD.

Study groups for one trial[38] were organized to compare a higher vs a lower dose for the same ILE, thereby permitting a combined analysis to address whether a lower dose of ILE was associated with PNALD risk. The lowest dose studied was 1 g/kg/day, and the highest dose was 3.5 g/kg/day. No significant difference in PNALD was found with a higher ILE dose vs lower ILE dose (RD = 0.0; 95% CI, −0.07 to 0.07; $P = 1$) (Figure 14). Therefore, the very low-quality evidence does not suggest a specific dose of ILE to use for the purposes of reducing the incidence of PNALD in preterm infants who are not expected to be exposed to PN for a prolonged duration. To provide context when considering what constitutes a prolonged duration, an example of a longer exposure to PN in relevant studies was a mean of 21 days.[19] A separate question in this guideline addressed whether ILE composition was associated with PNALD.

Question 7a: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, does reducing SO using any multicomponent-oil ILE reduce the incidence of PNALD?

Recommendation: For the purpose of preventing PNALD in preterm infants, we do not recommend any specific ILE composition.

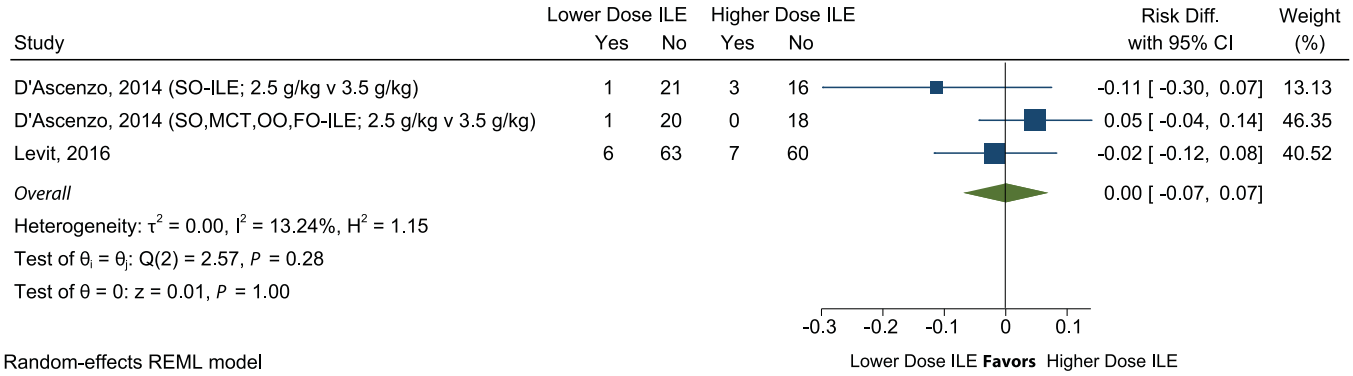

FIGURE 14 Risk difference in parenteral nutrition–associated liver disease in patients with higher vs lower ILE dose. Diff., difference; FO, fish oil; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; REML, restricted maximum likelihood; SO, soybean oil.

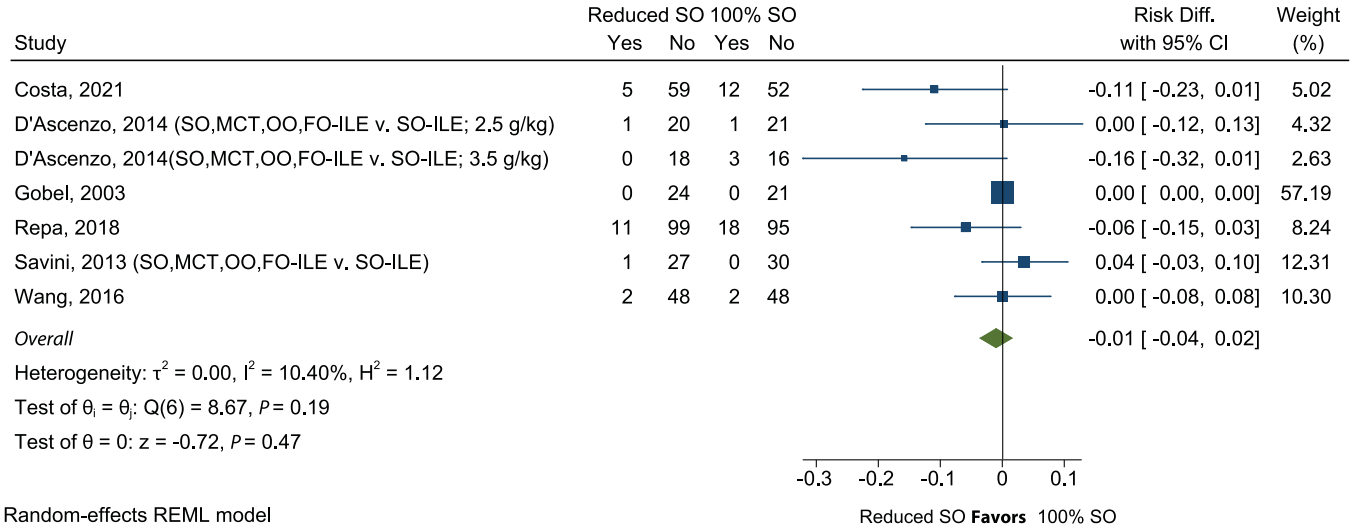

FIGURE 15 Risk difference in parenteral nutrition–associated liver disease in patients with an ILE containing 100% SO as the sole oil source vs any multicomponent-oil ILE. Diff., difference; FO, fish oil; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; REML, restricted maximum likelihood; SO, soybean oil.

We found no evidence of reduced PNALD risk with any specific ILE, whether it contains 100% SO as the sole oil source or a multicomponent-oil ILE with or without FO.

Quality of evidence: Low

Strength of recommendation: Strong

Rationale for recommendation: The development of this question took the vantage point that a reduction in the amount of SO in an ILE may be of clinical benefit. The trials included in this analysis utilized ILE with or without FO to reduce SO (Table 9).[30,32,33,38,40,41] Maximum ILE doses targeted were in the range of 3–3.5 g/kg/day. Two trials compared an ILE without FO to SO-ILE.[40,41] Using four groups, one trial compared the effects of different ILE doses as well as different ILE compositions. It was feasible to combine groups to compare different ILE compositions with the same ILE doses in that trial.[38] For that study, this led to a comparison of an SO reduction in part through a multicomponent-oil ILE that included FO. In addition, for a separate study with multiple groups,[33] not all groups could be included for comparison, since the control group could not be utilized multiple times. Therefore, based on a consensus decision, the groups selected for the comparison were those testing a multicomponent-oil ILE containing FO given its increased utilization in preterm infants.

In the combined analysis, the risk of PNALD was similar in groups whether using SO-ILE or any multicomponent-oil ILE (RD = −0.01; 95% CI, −0.04 to 0.02; $P = 0.47$) (Figure 15). Therefore, no specific ILE composition can be recommended for the purposes of preventing PNALD in this population.

Question 7b: In preterm infants, compared with an ILE containing 100% SO as the sole oil source, does reducing SO using a multicomponent-oil ILE that includes FO reduce the incidence of PNALD?

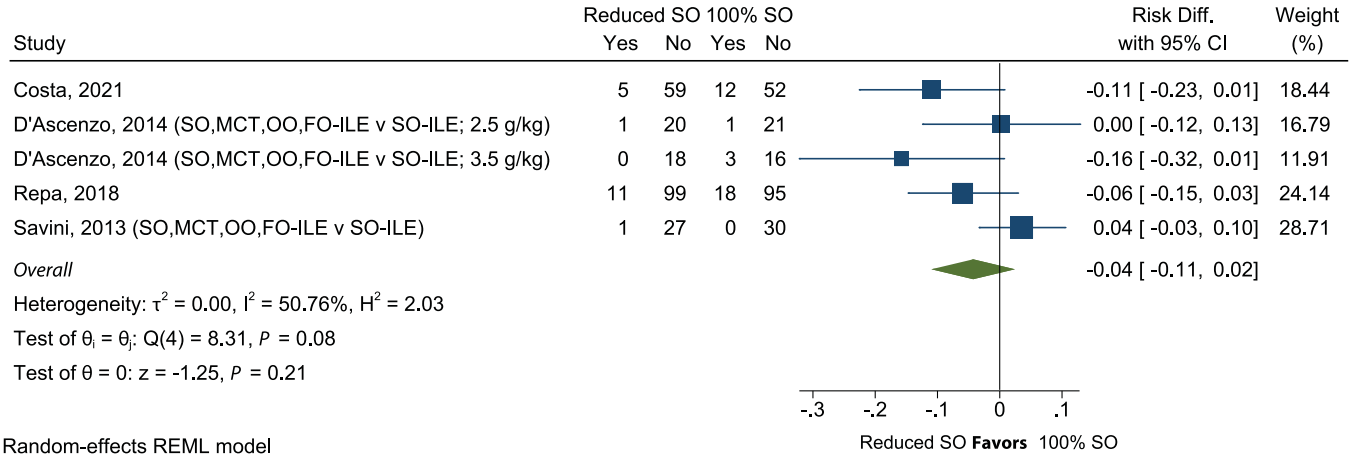

FIGURE 16 Risk difference in parenteral nutrition–associated liver disease in patients with an ILE containing 100% SO as the sole oil source vs only multicomponent-oil ILE which include FO. Diff., difference; FO, fish oil; ILE, lipid injectable emulsion; MCT, medium-chain triglyceride; OO, olive oil; REML, restricted maximum likelihood; SO, soybean oil.

Recommendation: For the purposes of preventing PNALD in preterm infants, we do not recommend the use of any specific ILE, whether it contains 100% SO as the sole oil source or a multicomponent-oil ILE that includes FO. As identified in the secondary analyses, further study is needed to evaluate the potential for an ILE containing FO and its association with ROP severity.

Quality of evidence: Low

Strength of recommendation: Strong

Rationale for recommendation: An original goal when developing questions related to PNALD was to make two distinct comparisons. The first comparison was between two ILE, one of which contained only SO and the other being any multicomponent-oil ILE with a lower SO content (question 7a). The second comparison was between SO-ILE and multicomponent-oil ILE with a lower SO content and FO (question 7b). While some overlap exists with question 7a, this second analysis involves a subset of studies to evaluate if an ILE that both reduces SO and provides FO reduces the risk of PNALD when compared with SO-ILE (Table 9). As determined by the combined analysis, PNALD risk was not different between groups (RD = −0.04; 95% CI, −0.11 to 0.02; $P = 0.21$) (Figure 16).

Secondary outcomes for 7a and 7b

Sufficient data were available for the combined analysis of secondary outcomes. Based on study design and predetermined outcomes, comparisons were available between SO-ILE and those that reduced SO with or without FO inclusion. One trial evaluated outcomes of interest, yet the interventions included changes in both AA and ILE dose, and the trial did not include a comparison group of infants exposed to SO-ILE.[57] Outcomes assessed were IVH, NEC, BPD, sepsis, ROP, length of stay, neurodevelopment, and mortality (Supporting Information: Table 8). When possible, two separate forest plots were created and included ILE under two conditions: (1) the multicomponent-oil ILE may or may not have included FO (ie, the ILE did not need to contain FO); or (2) only multicomponent-oil ILE containing FO was included. The only outcome for which two separate plots could be developed was IVH (Supporting Information: Figure 11–18).

The reduction of SO, in part through the inclusion of FO as an oil source, was associated with a decreased risk of ROP stage 3 or greater (RD = −0.04; 95% CI, −0.08 to −0.01; $P = 0.02$) (Supporting Information: Figure 16). The outcome of ROP was not significantly different in any individual trial. As with the primary questions, this combined analysis was accomplished by grouping appropriate comparisons within clinical trials with more than two intervention groups.[27,38] No studies that compared SO-ILE to a multicomponent-oil ILE without FO were included in this analysis. This analysis does not define the mechanism by which a multicomponent-oil ILE with FO alters ROP risk. No other secondary clinical outcomes evaluated through a combined analysis were significantly different between groups. When assessing the trials individually for these outcomes, there were no significant differences between groups. This supports the need for research investigating a multicomponent-oil ILE with FO to decipher whether the risk of severe ROP is truly reduced and, if so, the mechanism of action.

Question 8: In preterm infants, does reducing the dose of ILE reduce levels of unbound bilirubin?

Recommendation: We are unable to recommend any specific ILE dose for the purpose of reducing unbound bilirubin levels. We suggest further research utilizing clinical trials is needed to address this question.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: No RCTs evaluated met standards and definitions for inclusion to address this question, which was intended to evaluate the effects of ILE dose and unbound bilirubin concentrations. Select conditions (eg, when the ILE dose exceeds an infant's endogenous metabolic capacity) may be appropriate for

reducing ILE doses to mitigate increases in unbound bilirubin. With the current very low quality of evidence, insufficient information exists to inform any recommendation of ILE dose and in which circumstances such action is warranted. Given the potential concern of bilirubin encephalopathy with elevated unbound bilirubin and considering the potential for slower growth with ILE dose reduction, further research is needed to determine when ILE dose alterations may be appropriate to reduce unbound bilirubin levels, the risk of bilirubin encephalopathy, and neurodevelopmental impairment in the preterm infant.

Question 9: In preterm infants, does a reduced dose of ILE reduce the risk of sepsis?

Recommendation: We recommend against a dose reduction of ILE to prevent sepsis.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: While more trials evaluated the effects of ILE composition on sepsis risk, only one study evaluated the effects of a higher vs a lower dose of the same ILE (Table 10).[39] Sepsis was not different between groups. While a separate trial evaluated sepsis, the intervention also included alterations in AA and dextrose doses and therefore cannot inform any recommendation specific to this question.[20] Since reducing ILE provides fewer nonprotein calories, we recommend against ILE dose reduction for sepsis prevention in preterm infants given the importance of meeting a preterm infant's energy requirements and a current lack of evidence suggesting a benefit from dose reduction.

Question 10: In preterm infants, does providing parenteral micronutrients improve growth outcomes and reduce the risk for morbidities?

Recommendation: Given the paucity of available data from clinical trials, we recommend that micronutrient provisions, including calcium and phosphate prescribing, be in accordance with doses advised in consensus guidelines such as those provided by ASPEN and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).[1–3]

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: In considering the specific definition of micronutrients utilized for these guidelines, intervention trials involving five parenteral nutrients could be evaluated: acetate,[42] carnitine,[43,44,46] glutamine,[47,48] manganese,[49] and iron (with or without erythropoietin).[50–52] Prematurity-associated morbidities of primary interest included osteopenia of prematurity, BPD, and sepsis. For this question, both primary and secondary outcomes including growth were included in Table 11. No studies evaluated osteopenia of prematurity as a specific outcome associated with a specific micronutrient, mineral supplementation, or dose variation.

Providing carnitine was not associated with the risk of BPD (RD = 0.02; 95% CI, −0.12 to −0.16; $P = 0.76$) (Figure 17).

The outcome of sepsis was evaluated in single trials of carnitine,[43] glutamine,[47] and manganese,[49] with no difference between groups. One trial of manganese[49] evaluated BPD with no difference between groups. Outcomes were not different between acetate and chloride use in conjunction with sodium. In a single trial of carnitine supplementation,[43] days to regain BW were fewer with carnitine. In another trial, growth measurements obtained closer to discharge did not suggest a benefit from carnitine.[44,46] Heterogeneity in intervention and outcomes reported prevented a combined analysis of iron intervention with or without erythropoietin.[50–52] Importantly, no harm was identified in these trials that evaluated micronutrients.

The clinical trials evaluated did not ultimately provide sufficient information to suggest a specific dose for any of these nutrients by which outcomes assessed will be altered. Therefore, based on this very low quality of evidence, an appropriate approach is to utilize consensus recommendations such as those provided by ASPEN[1] and ESPGHAN[2] until such information is available through clinical trials. Also, a worthwhile consideration is whether the inclusion of some micronutrients in PN is necessary at all. For example, manganese is a natural contaminant of many parenteral products. Therefore, most

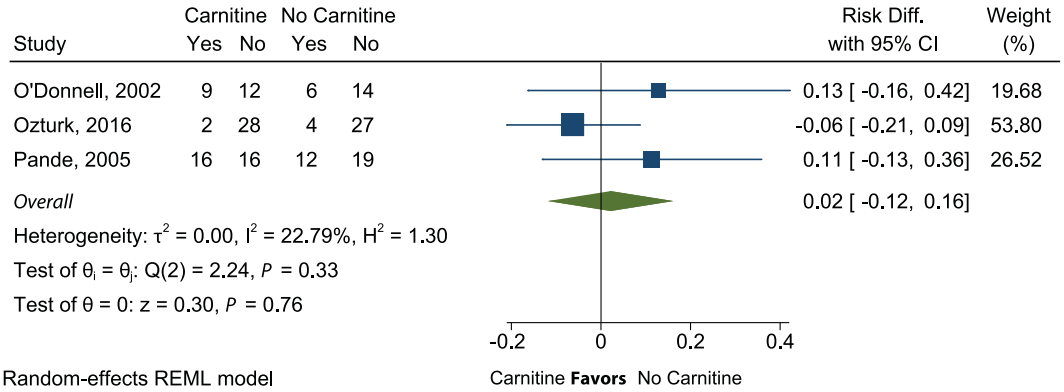

FIGURE 17 Risk difference in bronchopulmonary dysplasia in patients with carnitine vs no carnitine. Diff., difference; REML, restricted maximum likelihood.

neonatal PNs contain sufficient manganese to meet requirements for preterm infants without supplemental dosing.[61,62]

Question 11: In preterm infants, compared with customized PN solutions, are standardized PN solutions associated with growth outcomes?

Recommendation: Given the absence of clinical trials to evaluate this question, we do not recommend using standardized PN solutions for routine care of preterm infants. This recommendation does not address or dissuade the use of premade PN solutions utilized for the first 24 h after birth (commonly referred to as "starter" or "stock" PN), which are useful given their immediate availability at all hours.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: Customized PN solutions are those individually compounded to meet specific patient needs. These differ from standardized solutions, which are compounded in batches to contain the same nutrients and without regard to an individual clinical circumstance. No clinical trial met the standards and definitions for inclusion to address this question. Standardized PN solutions may reduce prescribing and administration errors and ensure that preterm infants receive the recommended doses of parenteral macronutrients and micronutrients. Additional study through clinical trials is warranted to determine if different PN solutions standardized for specific time periods show improved safety and efficacy while ensuring that the preterm infants' metabolic needs are met as measured through growth and development. The current lack of evidence through clinical trials does not allow for recommendation of standardized solutions. However, despite the lack of data from clinical trials, we acknowledge that the relative ease of implementing standardized solutions may be of value in low-resource settings.

Question 12: In preterm infants, does the use of insulin improve growth outcomes?

Recommendation: We recommend against the routine use of insulin for the purposes of improving growth outcomes in hospitalized preterm infants.

Quality of evidence: Very low

Strength of recommendation: Strong

Rationale for recommendation: This guideline question addresses the multifactorial occurrence of hyperglycemia in preterm infants shortly after birth when infants are receiving primarily PN and no to minimal enteral nutrition. A single study appropriate for inclusion evaluated utilizing insulin to maintain blood glucose in two distinct target ranges (Table 12). Of the multiple measures of growth, a smaller decline in head circumference SDS from birth through 36 weeks or discharge occurred for infants who maintained a lower glucose range. However, measurements were confined to the initial hospitalization. Adverse metabolic sequelae are associated with insulin, including hypoglycemia, increased lactate, acidosis, and reduced protein synthesis.[63] No long-term neurodevelopmental benefit has been documented with insulin use. For these reasons, we do not recommend routine use of insulin to improve growth outcomes.

FUTURE RESEARCH DIRECTIONS

In order to improve the safety of PN and determine how specific PN constituents alter clinical outcomes in preterm infants, future research should address the following limitations and knowledge gaps:

1. A major limitation to the inclusion of relevant clinical trials is the heterogeneity in defining outcomes. In fact, many published trials did not specify definitions of outcomes, raising the potential for bias. The field of neonatal nutrition should work together to specify and utilize meaningful and widely acceptable clinical outcomes, including biochemical measurements, so that reporting in neonatal nutrition studies is consistent. This may facilitate defining circumstances of toxicity vs safety. An additional consideration includes reporting continuous measures using more than one measure of central tendency (eg, both median and mean) and variance (eg, both interquartile range and standard deviation), perhaps as supplemental data, to facilitate combined future analyses.
2. Limitations in interpreting the effects of PN interventions result from an inability to account for the influence of enteral nutrition and must be acknowledged, particularly for outcomes measured later in a hospitalization (eg, BPD) and postdischarge (eg, growth and neurodevelopment). Also, heterogeneity exists in definitions of full feedings, which directly impacts the duration of PN. Future research can consider whether trajectories of illness and/or growth established during PN exposures may be modified by enteral nutrition.
3. As life-sustaining measures are provided more frequently to infants born at earlier gestational ages (ie, 22–23 weeks of gestation), investigation of PN dosing regimens specifically for these premature infants is warranted.
4. Reconsideration of a more unifying definition of EFAD and subsequent testing to determine specific doses for specific ILEs that are associated with an EFAD.
5. Ongoing attention to the following areas is needed: AA dose and risk of neurodevelopmental impairment including cerebral palsy, as well as ILE composition and potential mechanisms of protection against severe ROP.
6. Further research is warranted to define the clinical circumstances in which the risk of bilirubin encephalopathy is increased by ILE displacement of bilirubin as well as implementation of clinical trials to test ILE doses that may reduce encephalopathy risk.
7. It is unknown whether certain conditions of metabolic stress (eg, sepsis, NEC) may in fact be periods of time in which the infusion of nutrients only adds metabolic stress to the critically ill infant, based on current literature. Whether there are suitable times in which pausing PN or reducing doses of specific parenteral macronutrients or micronutrients is metabolically advantageous

has yet to be studied. While likely challenging to devise such studies, it is unknown if PN or specific parenteral constituents during times of critical illness may be associated with adverse outcomes specifically in preterm infants.

8. Similar guidelines should be considered for neonates, whether born preterm or at term, with congenital or acquired gastrointestinal disorders requiring surgery.

AUTHOR CONTRIBUTIONS

Daniel T. Robinson, Kara L. Calkins, Yimin Chen, M. Petrea Cober, Gustave H. Falciglia, and Timothy Sentongo contributed to the conception and design; Daniel T. Robinson, Kara L. Calkins, Yimin Chen, M. Petrea Cober, Gustave H. Falciglia, and Timothy Sentongo contributed to the acquisition of data; Liam McKeever, David D. Church, and Jacob Mey performed the analysis; all authors contributed to data interpretation; Daniel T. Robinson drafted the manuscript; all authors critically revised the manuscript; all authors gave final approval of this manuscript; all authors agree to be accountable for all aspects of this work ensuring integrity and accuracy.

CONFLICT OF INTEREST STATEMENT

Daniel T. Robinson received compensation for serving as a member of the Data Safety Monitoring Board for a clinical investigation sponsored by Fresenius Kabi. Daniel T. Robinson received research support from Fresenius Kabi. M. Petrea Cober currently receives compensations for serving as a consultant for BBraun/CAPS, Baxter, Fresenius Kabi, and Wolters Kluwer. Jacob Mey reports ownership in Cake Nutrition, LLC (Private Practice Dietetics). Kara L. Calkins currently receives support from Fresenius Kabi and Baxter as a consultant. Kara L. Calkins received compensation from Fresenius Kabi for serving as a speaker. Kara L. Calkins has received research support from Fresenius Kabi. Kara L. Calkins received compensation for serving as a member of the Data Safety Monitoring Board for a clinical investigation sponsored by Prolacta. Kara L. Calkins received compensation for serving on advisory board sponsored by Mead Johnson. Daniel T. Robinson and Kara L. Calkins serve as institutional principal investigators, with no salary funding, for a consortium database sponsored by Mead Johnson Nutrition. Gustave H. Falciglia has received a small business technology transfer grant (STTR) with Medical Predictive Science Corporation (MPSC) through the National Institutes of Health. He does not have a financial relationship with MPSC outside the grant.

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Note: Reference 64 to 71 are cited in Supporting information Tables.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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