Growth and Nutrition in Children with Established Bronchopulmonary Dysplasia: A Systematic Review

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Abstract

Introduction: Bronchopulmonary dysplasia (BPD) remains the most common late morbidity of preterm birth. Ongoing clinical care and research have largely focused on the pathogenesis and prevention of BPD in preterm infants. However, preterm infants who develop BPD have significant medical needs that persist throughout their neonatal intensive care unit course and continue post-discharge, including those associated with growth and nutrition. The objective of this study was to systematically review the available literature on nutrition and growth in infants with established BPD and to identify the knowledge and research gaps to provide direction for future studies. Methods: We conducted a systematic literature search in accordance with PRISMA guidelines using Ovid MEDLINE, CINAHL and Embase. Titles, abstracts, and full texts were independently reviewed by the authors and selected based on predetermined inclusion/exclusion criteria. Results were summarized qualitatively. Results: Excluding duplicates, 1,949 articles were identified. Of these, 36 articles were selected for inclusion. We identified the following key components of nutrition support and clinical care: Energy Expenditure, Growth and Metabolism; Enteral Nutrition; Supplements; Parenteral Nutrition; Respiratory Outcomes. Conclusions: Despite a large body of literature describing the role of growth and nutrition in the prevention of BPD, research is lacking with respect to interventions and management in the established BPD population. Thus, organized approaches for clinical interventions and trials with respect to growth and nutrition in infants and young children with established BPD are needed. These studies should include multiple centers, due to the small numbers of patients with BPD at each site.

Introduction

Due to advances in perinatal care, the survival of extremely preterm infants has dramatically improved in the recent years[1]. Preterm birth is associated with several adverse health consequences that contribute to neonatal morbidity and mortality, with respiratory complications being the primary source of poor outcomes[2]. Bronchopulmonary dysplasia (BPD) remains the most common late morbidity of preterm birth[2,3]. Ongoing clinical care and research have largely focused on issues regarding the pathogenesis and prevention of BPD in preterm infants with the goal of reducing the incidence of BPD[4]. However, preterm infants who develop BPD have significant medical needs that persist throughout their neonatal intensive care unit (NICU) course and continue post-discharge. Children with BPD have increased energy expenditure compared to preterm infants without BPD[5,6]. This is likely due to increased work of breathing[7], growth suppression from chronic stress and inflammation[8], and chronic steroid or diuretic use. Moreover, feeding could be impaired by oral aversion, intolerance, and gastroesophageal reflux disease.

Despite these identified issues and the known importance of growth and nutrition in other chronic lung diseases[9-11], there is limited research focusing on nutrition in infants with established BPD. The objective of this study was to systematically review the available literature on nutrition and growth in infants with established BPD and to identify the knowledge and research gaps to provide direction for future studies.

Methods

Literature Search

Ovid MEDLINE, CINAHL, and Embase were searched on September 3, 2020, using a comprehensive search strategy in accordance with PRISMA guidelines[12]. Search terms were developed through discussion among the authors, based on search terms in previous studies, and through consultation with an experienced medical librarian. The following search terms were used: "bronchopulmonary dysplasia" or "lung dysplasia" and "nutrition" or "growth."

Two authors (SEB, AIC) reviewed titles of all articles returned by the initial search, as well as the bibliographies of relevant review articles to identify which articles would be read in full. Once included studies were identified, their bibliographies and citation indices were also reviewed to identify additional studies.

The initial screening of titles and abstracts was performed by two independent reviewers (SEB, AIC). Articles were excluded if they did not include patients with BPD. Full texts of the remaining articles were independently reviewed (SEB, AIC, KAH, CPBV) to determine whether articles met the complete predetermined inclusion/exclusion criteria mentioned below, with disagreements between the reviewers settled after discussion.

Eligibility

The PICO model was used to select inclusion criteria, which included: 1. Population: patients who were born at < 32 weeks gestational age who were diagnosed with BPD; 2. Primary intervention: nutrition assessment and intervention; 3. Comparison: infants without BPD; 4. Outcomes: growth, pulmonary function, morbidity and mortality.

Studies were excluded if they met the following criteria: studies that did not include human subjects; studies only reporting developmental measures and outcomes; any study involving prenatal exposures and maternal interventions; studies that were not written in English; review articles; published abstracts without full text publications or without the full text available; and case study reports containing < 5 participants.

Results

Results of the Search

After removing duplicates, 1,949 unique articles were identified through the electronic database searches. Of these, 317 articles were identified for full text review. 281 articles did not meet the inclusion/exclusion criteria and were subsequently excluded. Finally, 36 articles were selected for inclusion. (Figure 1) Based on the selected literature, we used the identified key components of nutrition support and clinical care within established BPD: Energy Expenditure, Growth, and Metabolism; Enteral Nutrition; Supplements; Parenteral Nutrition; Respiratory Outcomes.

Energy Expenditure, Growth, and Metabolism

Infants with BPD have significantly higher total energy expenditure compared to infants without BPD[6,13]. Total daily energy expenditure has been found to be 16% greater in infants with BPD compared to matched controls[13]. Additionally, among infants with established BPD, the energy expenditure is strongly associated with respiratory rate and FiO2[13]. In their study, De Meer et al. found that infants with BPD require an additional 7.5 kcal/kg/day for every additional 10 breaths/min greater than 60 breaths/min[14].

Bott et at. evaluated the use of prediction equations versus direct calorimetry in children 4-10 years of age with BPD. They found that of the four prediction equations evaluated, all underestimated the resting energy expenditure. However, this difference was not statistically significant. The authors suggest that the prediction equations could be useful tools from a practical standpoint for predicting energy requirements in children with BPD[15].

Infants with BPD tend to be of smaller stature compared to infants without BPD[16]. A diagnosis of BPD has been associated with increased risk of low length at 12 months corrected gestational age[17]. In the same article, Lehtinen et al. found that weight and BMI at 36 weeks corrected gestational age were significantly

lower in infants with BPD compared to infants without BPD (p=0.058, p=0.018 respectively)[17]. By 3 months corrected gestational age, the growth differences between BPD and non-BPD infants had faded[17]. While growth was not associated with energy or macronutrient intake, the duration of ventilator therapy was found to be a risk factor for poor growth[17].

Greer et al. compared 16 very low birth weight infants with BPD to 16 very low birth weight infants without BPD matched for gestational age and found no differences in energy, calcium, vitamin D, or phosphorous intake in the first 60 days of hospitalization nor any significant difference in weight, length, head circumference, or bone mineral content at 12 months of age between the 2 groups[18].

Enteral Nutrition

There is limited and mixed data describing enteral nutrition in the setting of established BPD. Huysman et al. noted infants with BPD had impaired growth and body composition compared to healthy term infants of the same corrected gestational age[19]. In this BPD cohort, no correlation was found between outcomes and energy or protein intake. Theile et al. compared a current cohort of BPD patients to a cohort 10 years prior. They noted the current BPD cohort had improved growth and less days of mechanical ventilation. The difference between these cohorts correlated with earlier enteral feeds, increased protein intake, and decreased time to full feeds[20].

In the setting of BPD, use of breast milk in relation to outcomes has shown further mixed results. Kim et al. found an increased duration of breast milk intake was associated with decreased emergency department visits and need for systemic steroids for patients 36 months of age and younger with BPD[21]. In contrast, Acuña-Cordero et al. found that breastfeeding was only associated with decreased hospitalizations in female patients[22].

When studying formula supplementation and outcomes, various strategies have been investigated in the setting of BPD. Puango et al. found that 30 kcal/oz ready-to-feed toddler formula or fortified preterm formula were similarly tolerated with similar growth in older infants with BPD[23]. Pereira et al. compared a high-fat formula to a high-carbohydrate formula in patients with BPD[24]. They found a lower carbon dioxide (CO2) production rate in the high fat group, although there was no difference in other respiratory outcomes and the high fat group had decreased weight gain. The authors suggest that some of this lack of weight gain may be due to altered fat digestion and absorption observed in patients with BPD[25]. Gianni et al. showed that infants had improved weight gain with a change in fortification strategy an increase in calorie intake[26]. Fewtrell et al., however, compared infants receiving 24 kcal/oz formula at a goal of 180 ml/kg/d versus 30 kcal/oz formula at 145 ml/kg/d. They noted an increase in energy and protein intake in the 30 kcal group, but no difference in growth parameters[27]. Brunton et al. investigated a standard formula compared to formula fortified with protein and minerals in patients with BPD[28]. They found an increased nitrogen and mineral retention in the enriched formula group, associated with an increased length, bone mineral content, and lean mass. Although the two groups had similar absorption of calcium, zinc, and nitrogen; the enriched formula group had an increased absorption of phosphorus[28]. Hicks et al. also showed that infants with BPD had similar calcium absorption compared to infants without BPD[29].

Further considerations with regards to enteral intake and BPD include route and timing of feeding. Jensen et al. studied transpyloric versus gastric feeding in infants with BPD[30]. In their population they noted that transpyloric feeds were associated with increased frequency of hypoxemia.

Supplements

There were a number of studies examining the role of various supplements, particularly the role of vitamin A, in the development of BPD and its use as an intervention to prevent BPD. However, only two studies were identified which focused on infants with established BPD. Both studies evaluated the role of zinc in infants with established BPD. Vazquez-Gomis et al. found that serum zinc levels collected at 37-41 weeks corrected gestation age where significantly lower in infants with BPD compared to infants without BPD (p 0.005)[31]. In a retrospective chart review, Shaikhkalil et al. found that enteral zinc supplementation for a minimum of

14 days in extremely-low-birth-weight infants with BPD with a low rate of weight gain, despite optimization of energy and protein intake, had statistically significant increases in both average weight gain and rate of linear growth. Furthermore, 6 weeks after supplementation the increases in weight gain and linear growth remained significant[32].

Parenteral Nutrition

Parenteral nutrition (PN) is typically a key component of early nutritional management in infants at risk for BPD. Continued need for PN in infants with established BPD may coincide with a diagnosis of intestinal failure. Pediatric intestinal failure (IF) is defined as the need for PN for more than 60 days secondary to intestinal disease, dysfunction, or resection[33]. The most common cause of pediatric IF is surgical short bowel syndrome (SBS), including SBS caused by necrotizing enterocolitis[34]. A diagnosis of BPD and IF may change or affect the approach to various aspects of PN management including fluid volume, glucose infusion, and intravenous lipid management.

The increased caloric needs of patients with established BPD are challenging to achieve with parenteral nutrition. General principles regarding IV lipid provision in patients with established BPD include appropriate dosing of IV lipid to promote growth and avoidance of excess glucose infusion. However, concern exists regarding the role of IV lipid and the development of cholestasis and liver injury in infants. The development of cholestasis secondary to parenteral nutrition may be referred to as PNAC (parenteral nutrition associated cholestasis) or IFALD (intestinal failure associated cholestasis) when associated with IF. In the setting of prolonged PN administration or IF, IV lipid or dosing may be altered to prevent[35] or reverse[36] cholestasis. This may include lipid dosing at lower levels typical for age or the use of non-soy-based lipid emulsions[37] (Table 1).

Respiratory Outcomes

Several studies have shown that school children[38,39]and adolescents[40] with a history of BPD exhibit persistent lung function abnormalities when compared with matched controls born at term. In addition, there was no lung function catch-up during the first 2 years of life in infants born preterm[41,42].

A study of children with BPD by Bott et al.[43] showed that undernutrition before the age of 2 years is associated with hyperinflation (defined as Functional Residual Capacity$>$ 120%) later in childhood. The authors suggested that nutritional intervention should be performed before that age in order to prevent lung sequelae later in childhood. Another study[42] showed that infants with BPD who had better somatic weight gain velocity had significantly greater improvements in forced vital capacity (FVC), forced expiratory volume in 0.5 seconds ($FEV_{0.5}$), total lung capacity(TLC) and residual volume/total lung capacity(RV/TLC) z-scores; again suggesting a close relationship between the improved growth and lung function before 2 years of age. Similarly, a recent study by Panagiotounakou et al.[44] identified no significant difference in FEV1 and FVC at 8 years of age between term and preterm neonates who received “aggressive” nutrition during the NICU stay. This study also did not show any difference between comparison groups in lower respiratory tract infections and re-hospitalization due to them. Another study showed that an increase in height velocity is the main anthropometric measurement associated with the improvement of lung function but not an increase in weight in grams per day[45].

Van Mastrigt E et al.[46] studied 49 preterm infants born [?]32 weeks gestational age with severe BPD and found that weight at 6 months corrected age was independently associated with more normal lung volumes and less severe oxygen desaturations during sleep. Trzaski et al.[47] performed a similar retrospective study to identify factors associated with readiness to discontinue supplemental oxygen and to gain weight in infants with BPD approaching NICU discharge. The researchers identified four challenge-day variables and one factor from the medical history associated with the ability to consistently maintain oxygen saturations in room air through different stages of rest, activity, and feeding while maintaining appropriate weight gain. Increasing weight at time of challenge was associated with increased adjusted odds of passing the room air challenge. Increasing capillary pCO2, nasal cannula flow rate, and pulmonary acuity score as well as history of PDA ligation increased odds of challenge failure.

Discussion

Nutrition and growth in early lung development are important. Animal studies have revealed that alveolar formation is dysregulated by restricted nutrition[48]. Malnutrition was shown to reduce lung weight, lung weight-to-birth-weight ratio, lung volumes, as well as the number of alveoli and elastic fibers and collagen deposition. Hyperoxia reduced alveolar number and led to increased values of septal thickness and mean linear intercept. Combined, malnutrition and hyperoxia caused a more drastic reduction in alveolar number and collagen deposition[49]. In addition, postnatal growth restriction augmented oxygen-induced pulmonary hypertension[50].

Several studies demonstrated early postnatal growth restriction in preterm infants, especially in those with BPD[16,51]. Growth restriction has an effect on both total body fat and fat free mass[52]. DeRegnier et al. found that by 2-4 weeks of age infants with BPD had lower weight, length, and head circumference z-scores, as well as arm muscle area and arm fat area measurements, compared to infants without BPD matched for gestational age and birth weight[16]. Furthermore, infants with BPD at 12 months post-term age, compared to healthy term infants, had a significantly lower weight, length, fat free mass, and total body fat, despite having energy and protein intake at or above the recommended daily intake for healthy term infants during the first six months after correcting to term[52].

Pulmonary function is altered in all preterm infants, but infants with BPD have lower lung functions than those without BPD at two different time points 1 year apart[45]. A systematic review and meta-analysis[53] concluded that FEV1 is diminished in both ex-preterm subjects with and without BPD at the age of 5-23 years. It is also widely shown that the nutritional status of these children at two years of age influences nutrition and respiratory outcomes later on during childhood[43,54]. In addition, increase in length is closely associated with an increase in lung function[55]. Clinical symptoms of infants with BPD often improve gradually with advancing age during childhood (ages 1 to 12 years)[56]. However, longitudinal measures of infant lung function showed little change with growth, with abnormalities in forced expiratory flow, lung volume, and compliance persisting over time[42,57]. Similarly, recent studies in school age children demonstrated persistent abnormalities in small airway function in children with BPD[58-60]. Long-term changes in pulmonary function, specifically airway obstruction, have also been described in young adults with a history of BPD[61].

Consistent with American Academy of Pediatrics (AAP) recommendations[62], mother's breast milk should be used through the first 6 months of life. Adequate protein intake is necessary to promote linear growth, lung growth, and repair of damaged tissue[63]. At present, there are no specific protein intake recommendations for infants with BPD. However, the AAP recommends 3.2 to 4.5 g/kg/d of enteral protein for preterm infants[64]. Although excessive calories may increase CO2 production, past studies implicate a dietary imbalance of high carbohydrate to low fat that is particularly problematic in children and adults with chronic respiratory failure. With respect to parental nutrition, care providers should monitor total fluid administration closely in patients with BPD on parenteral nutrition to avoid both fluid depletion and fluid excess. Fluid calculations should include both parenteral fluid and oral/enteral fluid. Oral and enteral fluid is typically comprised by feedings and water flushes. Patients require fluid administration to meet maintenance needs, which may need adjustment based on patient output (urine, stool), weight, and laboratory data (blood urea nitrogen, urinalysis) if available.

Few resources have focused on intravenous (IV) lipid strategies in infants with established BPD. The majority of literature has focused on the potential role of various IV lipid formulations and risk of BPD development. A mixed lipid emulsion containing soy, medium-chain triglycerides, olive, and fish oils has been associated with a reduced risk of BPD development[65]. However, studies have also shown only reduced severity of BPD[66] or no change in risk of BPD development[67] with this lipid mix use. The exact role of non-soy-based lipid emulsions in the modulation of BPD risk is unclear. This may be related to differences in experimental design and patient populations of studies evaluating this topic. If lipid dosing is reduced below typical dosing of 2.5-3 gm/kg/day, infants may require an increase in parenteral nutrition glucose infusion rate (GIR) to provide sufficient caloric intake. This may pose a risk for increased CO2 production should GIR become excessive. CO2 is a byproduct of aerobic oxidation produced during the metabolism of glucose. Due to this,

high GIRs above standard 10-14 mg/kg/min should be avoided if possible in infants with BPD at risk for CO2 retention[68]. However, children should still receive appropriate GIR for calorie needs and glucose should not be limited.

Overall, these various studies show that differences exist between patients with BPD and other neonates, and that nutrition can influence some of these outcome differences. Many of the studies included in this section had small sample sizes, at times limiting the findings or interpretation of the data. The available data, however, leads to noticeable gaps in our understanding, including the ideal approach to nutrition for patients with BPD. Frequent weight measurements as well as accurate length measurements are needed. In addition, once the infant is able to tolerate enteral feeds, evaluation for aspiration is needed to assure intact swallow mechanisms. If swallow dysfunction is identified, then alternative routes of enteral feeding should be considered, such as nasogastric tubes or transcutaneous gastrostomy. Given these complexities, recommendations are for an interdisciplinary approach for the care of patients with established BPD[63].

In conclusion, while there exists a large body of literature related to the role of growth and nutrition in the prevention of BPD, research is lacking with respect to interventions and management in the established BPD population. Thus, organized approaches for clinical interventions and trials with respect to growth and nutrition in infants and young children with established BPD are needed. These studies should include multiple centers, due to the small numbers of patients with BPD at each site.

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References

1. Stoll BJ, Hansen NI, Bell EF, et al. Trends in care practices, morbidity, and mortality of extremely preterm neonates, 1993-2012.*JAMA.* 2015;314(10):1039-1051.

2. Patel RM. Short and long-term outcomes for extremely preterm infants.*Am J Perinatol.* 2016;33(3):318.

3. Bancalari E, Gerhardt T. Bronchopulmonary dysplasia. *Pediatr Clin North Am.* 1986;33(1):1-23.

4. McEvoy CT, Jain L, Schmidt B, Abman S, Bancalari E, Aschner JL. Bronchopulmonary dysplasia: NHLBI workshop on the primary prevention of chronic lung diseases. *Annals of the American Thoracic Society.*2014;11(Supplement 3):S146-S153.

5. Denne SC. Energy expenditure in infants with pulmonary insufficiency: is there evidence for increased energy needs? *The Journal of nutrition.* 2001;131(3):935S-937S.

6. Yeh TF, McClenan DA, Ajayi OA, Pildes RS. Metabolic rate and energy balance in infants with bronchopulmonary dysplasia. *J Pediatr.*1989;114(3):448-451.

7. Lui K, Lloyd J, Ang E, Rynn M, Gupta JM. Early changes in respiratory compliance and resistance during the development of bronchopulmonary dysplasia in the era of surfactant therapy. *Pediatr Pulmonol.*2000;30(4):282-290.

8. Balinotti JE, Chakr VC, Tiller C, et al. Growth of lung parenchyma in infants and toddlers with chronic lung disease of infancy.*American Journal of Respiratory & Critical Care Medicine.*2010;181(10):1093-1097.

9. Sanders DB, Fink A, Mayer-Hamblett N, et al. Early life growth trajectories in cystic fibrosis are associated with pulmonary function at age 6 years. *The Journal of pediatrics.* 2015;167(5):1081-1088. e1081.

10. Lai HJ, Shoff SM, Farrell PM. Recovery of birth weight z score within 2 years of diagnosis is positively associated with pulmonary status at 6 years of age in children with cystic fibrosis.*Pediatrics.* 2009;123(2):714-722.

11. Konstan MW, Butler SM, Wohl MEB, et al. Growth and nutritional indexes in early life predict pulmonary function in cystic fibrosis.*The Journal of pediatrics.* 2003;142(6):624-630.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6(7):e1000097.

13. de Meer K, Westerterp KR, Houwen RH, Brouwers HA, Berger R, Okken A. Total energy expenditure in infants with bronchopulmonary dysplasia is associated with respiratory status. *Eur J Pediatr.*1997;156(4):299-304.

14. De Meer K, Westerterp KR, Houwen RHJ, Brouwers HAA, Berger R, Okken A. Total energy expenditure in infants with bronchopulmonary dysplasia is associated with respiratory status. *Eur J Pediatr.*1997;156(4):299-304.

15. Bott L, Beghin L, Marichez C, Gottrand F. Comparison of resting energy expenditure in bronchopulmonary dysplasia to predicted equation.*Eur J Clin Nutr.* 2006;60(11):1323-1329.

16. DeRegnier RAO, Guilbert TW, Mills MM, Georgieff MK. Growth failure and altered body composition are established by one month of age in infants with bronchopulmonary dysplasia. *J Nutr.*1996;126(1):168-175.

17. Lehtinen A, Korhonen P, Hyodynmaa E, et al. Adipokines played a limited role in predicting temporary growth differences between very low birthweight infants with and without bronchopulmonary dysplasia.*Acta Paediatr.* 2017;106(10):1583-1588.

18. Greer FR, McCormick A. Bone mineral content and growth in very-low-birth-weight premature infants. Does bronchopulmonary dysplasia make a difference? *Am J Dis Child.* 1987;141(2):179-183.

19. Huysman WA, de Ridder M, de Bruin NC, et al. Growth and body composition in preterm infants with bronchopulmonary dysplasia.*Archives of disease in childhood Fetal and neonatal edition.*2003;88(1):F46-51.

20. Theile AR, Radmacher PG, Anschutz TW, Davis DW, Adamkin DH. Nutritional strategies and growth in extremely low birth weight infants with bronchopulmonary dysplasia over the past 10 years. *J Perinatol.* 2012;32(2):117-122.

21. Kim LY, McGrath-Morrow SA, Collaco JM. Impact of breast milk on respiratory outcomes in infants with bronchopulmonary dysplasia.*Pediatric pulmonology.* 2019;54(3):313-318.

22. Acuna-Cordero R, Sossa-Briceno MP, Rodriguez-Martinez CE. Predictors of hospitalization for acute lower respiratory infections during the first two years of life in a population of preterm infants with bronchopulmonary dysplasia. *Early Hum Dev.* 2018;127:53-57.

23. Puangco MA, Schanler RJ. Clinical experience in enteral nutrition support for premature infants with bronchopulmonary dysplasia. *J Perinatol.* 2000;20(2):87-91.

24. Pereira GR, Baumgart S, Bennett MJ, et al. Use of high-fat formula for premature infants with bronchopulmonary dysplasia: metabolic, pulmonary, and nutritional studies. *J Pediatr.*1994;124(4):605-611.

25. Boehm G, Bierbach U, Moro G, Minoli I. Limited fat digestion in infants with bronchopulmonary dysplasia. *Journal of pediatric gastroenterology and nutrition.* 1996;22(2):161-166.

26. Gianni ML, Roggero P, Colnaghi MR, et al. The role of nutrition in promoting growth in pre-term infants with bronchopulmonary dysplasia: a prospective non-randomised interventional cohort study. *BMC Pediatr.* 2014;14:235.

27. Fewtrell MS, Adams C, Wilson DC, Cairns P, McClure G, Lucas A. Randomized trial of high nutrient density formula versus standard formula in chronic lung disease. *Acta Paediatr.*1997;86(6):577-582.

28. Brunton JA, Saigal S, Atkinson SA. Growth and body composition in infants with bronchopulmonary dysplasia up to 3 months corrected age: a randomized trial of a high-energy nutrient-enriched formula fed after hospital discharge. *J Pediatr.* 1998;133(3):340-345.

29. Hicks PD, Rogers SP, Hawthorne KM, Chen Z, Abrams SA. Calcium absorption in very low birth weight infants with and without bronchopulmonary dysplasia. *J Pediatr.* 2011;158(6):885-890.e881.

30. Jensen EA, Zhang H, Feng R, et al. Individualising care in severe bronchopulmonary dysplasia: a series of N-of-1 trials comparing transpyloric and gastric feeding. *Arch Dis Child Fetal Neonatal Ed.* 2020;105(4):399-404.

31. Vazquez-Gomis R, Bosch-Gimenez V, Juste-Ruiz M, Vazquez-Gomis C, Izquierdo-Fos I, Pastor-Rosado J. Zinc concentration in preterm newborns at term age, a prospective observational study. *BMJ Paediatr Open.* 2019;3(1):e000527.

32. Shaikhkhalil AK, Curtiss J, Puthoff TD, Valentine CJ. Enteral zinc supplementation and growth in extremely-low-birth-weight infants with chronic lung disease. *Journal of pediatric gastroenterology and nutrition.* 2014;58(2):183-187.

33. Merritt RJ, Cohran V, al e. Intestinal Rehabilitation Programs in the Management of Pediatric Intestinal Failure and Short Bowel Syndrome.*JPGN.* 2017:65: 588-596.

34. Duggan CP, Jaksic T. Pediatric Intestinal Failure. *N Engl J Med.* 2017:377: 666-375.

35. Nandivada P, Fell GL, Gura KM, Puder M. Lipid emulsions in the treatment and prevention of parenteral nutrition–associated liver disease in infants and children–. *The American journal of clinical nutrition.* 2016;103(2):629S-634S.

36. Cober MP, Killu G, Brattain A, Welch KB, Kunisaki SM, Teitelbaum DH. Intravenous fat emulsions reduction for patients with parenteral nutrition–associated liver disease. *The Journal of pediatrics.*2012;160(3):421-427.

37. Diamond IR, Grant RC, Pencharz PB, et al. Preventing the progression of intestinal failure–associated liver disease in infants using a composite lipid emulsion: a pilot randomized controlled trial of SMOFlipid. *Journal of Parenteral and Enteral Nutrition.*2017;41(5):866-877.

38. vom Hove M, Prenzel F, Uhlig HH, Robel-Tillig E. Pulmonary outcome in former preterm, very low birth weight children with bronchopulmonary dysplasia: a case-control follow-up at school age. *The Journal of pediatrics.* 2014;164(1):40-45. e44.

39. Cazzato S, Ridolfi L, Bernardi F, Faldella G, Bertelli L. Lung function outcome at school age in very low birth weight children.*Pediatr Pulmonol.* 2013;48(8):830-837.

40. Welsh L, Kirkby J, Lum S, et al. The EPICure study: maximal exercise and physical activity in school children born extremely preterm.*Thorax.* 2010;65(2):165-172.

41. Friedrich L, Pitrez PMC, Stein RT, Goldani M, Tepper R, Jones MH. Growth rate of lung function in healthy preterm infants. *Am J Respir Crit Care Med.* 2007;176(12):1269-1273.

42. Filbrun AG, Popova AP, Linn MJ, McIntosh NA, Hershenson MB. Longitudinal measures of lung function in infants with bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2011;46(4):369-375.

43. Bott L, Beghin L, Devos P, Pierrat V, Matran R, Gottrand F. Nutritional status at 2 years in former infants with bronchopulmonary dysplasia influences nutrition and pulmonary outcomes during childhood.*Pediatr Res.* 2006;60(3):340-344.

44. Panagiotounakou P, Sokou R, Gounari E, et al. Very preterm neonates receiving "aggressive" nutrition and early nCPAP had similar long-term respiratory outcomes as term neonates. *Pediatr Res.*2019;86(6):742-748.

45. Sanchez-Solis M, Garcia-Marcos L, Bosch-Gimenez V, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P. Lung function among infants born preterm, with or without bronchopulmonary dysplasia. *Pediatric pulmonology.* 2012;47(7):674-681.

46. van Mastrigt E, Kakar E, Ciet P, et al. Structural and functional ventilatory impairment in infants with severe bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2017;52(8):1029-1037.

47. Trzaski JM, Hagadorn JI, Hussain N, Schwenn J, Wittenzellner C. Predictors of successful discontinuation of supplemental oxygen in very low-birth-weight infants with bronchopulmonary dysplasia approaching neonatal intensive care unit discharge. *Am J Perinatol.*2012;29(2):79-85.

48. Joss-Moore LA, Hagen-Lillevik SJ, Yost C, et al. Alveolar formation is dysregulated by restricted nutrition but not excess sedation in preterm lambs managed by noninvasive support. *Pediatric research.*2016;80(5):719-728.

49. Mataloun M, Leone C, Mascaretti R, Dohlnikoff M, Rebello C. Effect of postnatal malnutrition on hyperoxia-induced newborn lung development.*Braz J Med Biol Res.* 2009;42(7):606-613.

50. Wedgwood S, Warford C, Agvateesiri SC, et al. Postnatal growth restriction augments oxygen-induced pulmonary hypertension in a neonatal rat model of bronchopulmonary dysplasia. *Pediatr Res.*2016;80(6):894-902.

51. Ehrenkranz RA, Younes N, Lemons JA, et al. Longitudinal growth of hospitalized very low birth weight infants. *Pediatrics.*1999;104(2):280-289.

52. Huysman WA, de Ridder M, de Bruin NC, et al. Growth and body composition in preterm infants with bronchopulmonary dysplasia.*Archives of Disease in Childhood Fetal & Neonatal Edition.*2003;88(1):F46-51.

53. Kotecha SJ, Edwards MO, Watkins WJ, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax.*2013;68(8):760-766.

54. Bott L, Beghin L, Hankard R, Pierrat V, Gondon E, Gottrand F. Resting energy expenditure in children with neonatal chronic lung disease and obstruction of the airways. *Br J Nutr.*2007;98(4):796-801.

55. Saarenpaa H-K, Tikanmaki M, Sipola-Leppanen M, et al. Lung Function in Very Low Birth Weight Adults. *Pediatrics.* 2015;136(4):642-650.

56. Baraldi E, Filippone M. Chronic lung disease after premature birth.*N Engl J Med.* 2007;357(19):1946-1955.

57. Robin B, Kim YJ, Huth J, et al. Pulmonary function in bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2004;37(3):236-242.

58. Doyle LW, Victorian Infant Collaborative Study G. Respiratory function at age 8-9 years in extremely low birthweight/very preterm children born in Victoria in 1991-1992. *Pediatr Pulmonol.*2006;41(6):570-576.

59. Brostrom EB, Thunqvist P, Adenfelt G, Borling E, Katz-Salamon M. Obstructive lung disease in children with mild to severe BPD.*Respir Med.* 2010;104(3):362-370.

60. Filippone M, Sartor M, Zacchello F, Baraldi E. Flow limitation in infants with bronchopulmonary dysplasia and respiratory function at school age. *Lancet.* 2003;361(9359):753-754.

61. Vollsaeter M, Roksund OD, Eide GE, Markestad T, Halvorsen T. Lung function after preterm birth: development from mid-childhood to adulthood. *Thorax.* 2013;68(8):767-776.

62. Eidelman AI. Breastfeeding and the use of human milk: an analysis of the American Academy of Pediatrics 2012 Breastfeeding Policy Statement.*Breastfeed Med.* 2012;7(5):323-324.

63. Abman SH, Collaco JM, Shepherd EG, et al. Interdisciplinary Care of Children with Severe Bronchopulmonary Dysplasia. *J Pediatr.*2017;181:12-28.

64. Nutrition ACo. *Pediatric Nutrition.* Elk Grove Village2020.

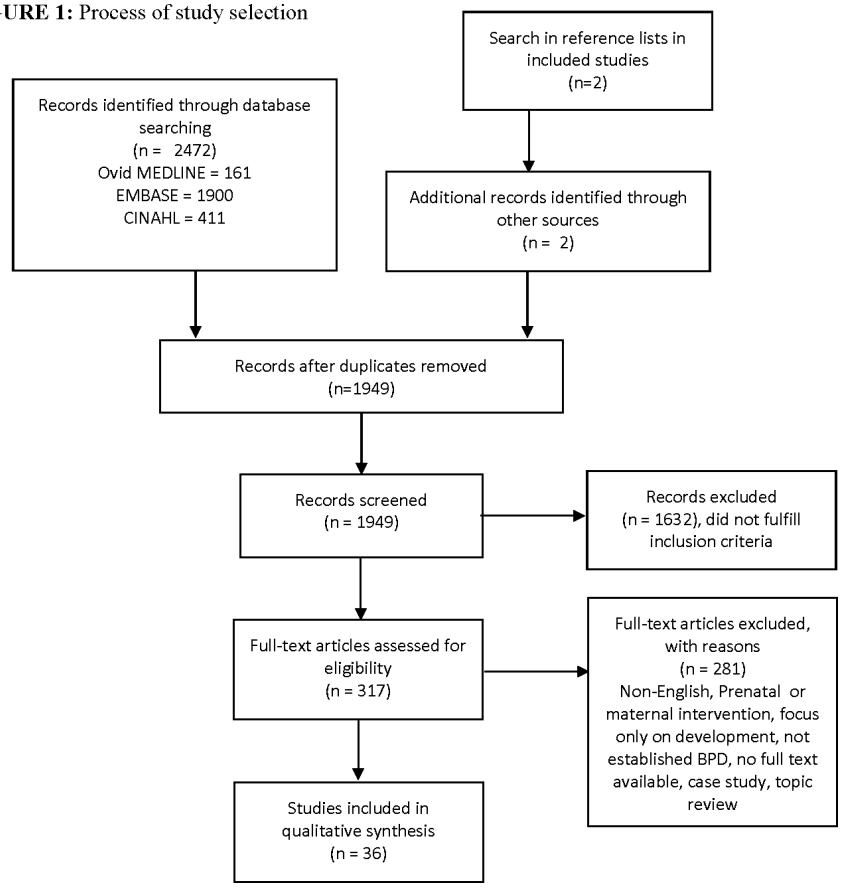
65. Skouroliakou M, Konstantinou D, al e. Cholestasis, Bronchopulmonary Dysplasia, and Lipid Profile in Preterm Infants Receiving MCT/n-3-PUFA-Containing or Soybean-Based Lipid Emulsions. *Nutr Clin Pract.* 2012:27(26): 817-824.

66. Uberos J, Jimenez-Montilla S, al e. Morbidity Outcomes of Very Low Birth Weight Neonates Receiving Parenteral Nutrition with Fish Oil Enriched Lipid Emulsions or Lipid Emulsion with Soybean Oil: An Observational Study. *Am J Perinatol.* 2020:epub.

67. Najm S, Lofqvist C, al e. Effects of a lipid emulsion containing fish oil on polyunsaturated fatty acid profiles, growth and morbidities in extremely premature infants: A randomized controlled trial. *Clin Nutr ESPEN.* 2017:20: 17-23.

68. Guidelines for the Use of Parenteral and Enteral Nutrition in Adult and Pediatric Patients. *JPEN.* 2002:26: 21SA-138SA.

FIGURE 1: Process of study selection



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