

# Effectiveness of Feeding Supplementation in Preterm Infants: An Overview of Systematic Reviews

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## Research article

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# Abstract

## Background

Preterm infants have higher nutrition needs than term infants. The effectiveness of various feeding supplementation was assessed by the improvement of health outcomes in single specific systematic reviews (SRs). The aim of this review is to summarise these SRs to provide comprehensive evidence on the effectiveness of these interventions for preterm infants.

## Methods

A literature search was conducted in the PUBMED, EMBASE, Science Direct, Cochrane library, Web of Science, and Wiley online library. SR selection followed clear inclusion and exclusion criteria. Data extraction was performed by using the pre-designed tables and quality assessment was done by the AMSTAR tool.

## Results

Seventeen SRs were included in the review. Fifteen kinds of feeding supplementation were reported in the SRs. The effectiveness of the interventions was defined as positive, having no impact, or inconclusive. Lactoferrin, probiotic, prebiotic, vitamin D, protein, and arginine were concluded to be positive; inositol, iodine, fat, glutamine, and long chain polyunsaturated fatty acid (LCPUFA) were concluded to have no impact; results for prebiotic (for prevention of hyperbilirubinaemia), carbohydrate, multi-nutrient, taurine, calcium, and phosphorus were inconclusive. All the SRs included were graded as being of high quality.

## Conclusions

Supplements with positive effects on health improvement were considerable to add to the feeding of preterm infants. More well-designed large RCTs are still needed to address the unsolved problems in the SRs concluded as having no impact or where the results were inconclusive.

# Introduction

Preterm infants, whose gestational age is less than 37 weeks, account for an increased risk of morbidity and mortality compared with term infants.(1) An estimated 15 million preterm infants are born each year, and the number is still increasing.(2) Prematurity results in developmental delay; in addition, underdeveloped body systems make the preterm infant vulnerable to multiple diseases such as necrotizing enterocolitis, late-onset sepsis, and respiratory distress syndrome which are all major contributors to death.(3–5)

Sufficient nutrition support is essential for the growth and development of infants while preterm neonates have an even higher requirement for nutrition support. The adequate nutrient supply helps them to build up their bodies, boosts their immune system, and fights various infections. Generally, mothers' milk has been proved to be the best food choice for neonates because it is full of nutritive and non-nutritive bioactive components.(6–8) Infant formula is also an effective substitute when breastfeeding is not available.(9) However, both of these might not meet the nutrition need of preterm infants considering their high demand. Extra supplementation of their feeding is apparently necessary.

Various kinds of feeding supplementation such as probiotics, lactoferrin and others have been tested in the primary studies, immaterial of whether they are RCTs or not, and some SRs have synthesised the relative evidence to assess the effects of supplementation. These SRs usually focussed on one particular supplement and different outcome assessment, which limited their ability to provide comprehensive evidence of the effectiveness of this feeding supplementation on growth improvement and disease prevention.

The aim of this review was to integrate and summarise the evidence from these SRs to provide a comprehensive description of this area. To the best of our knowledge, this is the first review that contains all the SRs of feeding supplementation assessment.

# Methods

This review was drafted with reference to the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.(10) Given that all the data had been published online, no ethical approval or patient consent was required.

# Search strategies

A systematic search was conducted up to May 2020 in the following mainstream databases: PUBMED, EMBASE, Science Direct, Cochrane library, Web of Science, and Wiley online library. There was no language restriction applied. The review question was framed into the PICO form, namely population, interventions, comparison, and outcomes. The population was preterm infant, with a low or very low birth weight. The interventions were designed to add extra supplements to the milk fed to the preterm infants. A series of health outcomes – such as physical and neurodevelopment – were assessed.

SRs were included if they met the following criteria: (1) participants were preterm infants; (2) SRs focused on the comparison of nutrient supplementation to breast milk or formula in order to observe its effects on health improvement; (3) SRs contained a meta-analysis of the preterm infants' outcomes and authors' conclusions. When two or more similar SRs appeared on one topic, the year of publication, the number of primary included studies, an assessment of health outcomes, and quality of the content were thoroughly evaluated in order to determine the best choice for inclusion.

The terms used in the search for potential SRs followed the PICO principle: ('preterm infant' OR 'premature infant' OR 'preterm neonate' OR 'low birth weight infant' OR 'very low birth weight infant') AND ('feeding supplementation' OR 'feeding supplement' OR 'supplement' OR 'feeding'). The article type was limited to systematic review, meta-analysis, or review.

## **Data extraction and analysis**

The data from each SR was extracted by using the predesigned data collection tables. Table 1 summarises the characteristics of the included studies which mainly contained the basic information of the research: author, year of publication, title, objective, study designs, number of included studies, and sample size. Table 2 summarises the characteristic of the interventions. Since different studies assessed different health outcomes and it was difficult to list them all in one small table, reviewers agreed to classify them into several aspects in order to display: (1) physical growth: short term (less than 12 weeks), long term (more than 12 weeks); (2) neurodevelopment: short term (less than 12 weeks), long term (more than 12 weeks); (3) biochemical outcomes; (4) other health outcomes (time to achieve full enteral feeding, hospital stay duration etc.); (5) morbidity of any disease; (6) all-cause mortality; and (7) effectiveness of the intervention.

Table 1  
Characteristic of the included studies

Author (Year)	Title of the study	Objectives	Study designs	No. of included studies/ Sample size
Pammi et al. (2020)	Enteral lactoferrin supplementation for prevention of sepsis and necrotizing enterocolitis in preterm infants	To assess the effect and safety of lactoferrin to prevent LOS and NEC in preterm neonates.	RCTs and quasi-RCTs	12/5425
Howlett et al. (2019)	Inositol in preterm infants at risk for or having respiratory syndrome	To assess the effectiveness and safety of supplementary inositol in preterm infants in reducing adverse neonatal outcomes.	RCTs and quasi-RCTs	3/1177
Walsh et al. (2019)	Iodine supplementation for the prevention of mortality and adverse neurodevelopment outcomes in preterm infant	To assess the evidence from RCTs that dietary supplementation with iodine reduces mortality and morbidity in preterm infants.	RCTs or quasi-RCTs	2/1394
Chi et al. (2019)	Effects of prebiotic on sepsis, necrotizing enterocolitis, mortality, feeding intolerance, time to full enteral feeding, length of hospital stay, and stool frequency in preterm infants: a meta-analysis	To assess the effects of prebiotics in promoting health or preventing adverse health outcomes in preterm infants.	RCTs	18/1322
Armannia et al. (2019)	Prebiotics for the prevention of hyperbilirubinaemia in neonates	To determine whether administration of prebiotics reduces the incidence of hyperbilirubinaemia among term and preterm infants.	RCTs or quasi-RCTs	3/154
Amissah et al. (2018)	Fat supplementation of human milk for promoting growth in preterm infants	To determine whether supplementation of human milk with fat to preterm infants improve a series of health outcomes without adverse effect.	RCT	1/14
Amissah et al. (2018)	Protein supplementation of human milk for promoting growth in preterm infants	To determine whether supplementation of human milk with protein to preterm infants improve a series of health outcomes without adverse effect.	RCTs or quasi-RCTs	6/204
Amissah et al. (2018)	Carbohydrate supplementation of human milk for promoting growth in preterm infants	To determine whether supplementation of human milk with Carbohydrate to preterm infants improve a series of health outcomes without adverse effect.	Quasi-RCT	1/75
Yang et al. (2018)	Effect of different dose of vitamin D supplementation on preterm infants –an updated meta-analysis	To assess the effect of vitamin D on body development, immune function and disease prevention in preterm infants.	RCTs	12/NR
Harding et al. (2017)	Calcium and phosphorus supplementation of human milk for preterm infants	To determine whether addition of calcium and phosphorus supplements to human milk leads to improved growth and bone metabolism of preterm infants.	RCTs and quasi-RCTs	1/40
Shah et al. (2017)	Arginine supplementation for prevention of necrotizing enterocolitis in preterm infants	To exam the effect of arginine supplementation on the incidence of NEC in preterm infants.	RCTs and quasi-RCTs	3/285
Aceti et al. (2017)	Probiotics prevent Late-onset sepsis in human milk-feed, very low birth weight preterm infant: systemic review and meta-analysis	To evaluate the effect of probiotics for LOS prevention in preterm infants.	RCTs	25/5868
Moe-Byrne et al. (2016)	Glutamine supplementation to prevent morbidity and mortality in preterm infants	To determine the effects of glutamine supplementation on mortality and morbidity in preterm infants.	RCTs and quasi-RCTs	12/2877
Moon et al. (2016)	Long chain polyunsaturated fatty acid supplementation in preterm infants	To assess whether supplementation of formula milk with LCPUFA is safe and of benefit to preterm infants.	RCTs	17/2260
AlFaleh et al. (2014)	Probiotics for prevention of necrotizing enterocolitis in preterm infants	To compare the efficacy and safety of prophylactic enteral probiotics administration in the prevention of NEC or sepsis in preterm infants.	RCTs or quasi-RCTs	24/5529
McCormick et al. (2010)	Multinutrient fortification of human breast milk for preterm infants following hospital discharge	To determine the effect of feeding with multi-nutrient fortified human breast milk on growth and development in preterm infants or low birth weight infant following hospital discharge.	RCTs or quasi-RCTs	1/39

NR, not reported.

Author (Year)	Title of the study	Objectives	Study designs	No. of included studies/ Sample size
Verner et al. (2007)	Effect of taurine supplementation on growth and development in preterm or low birth weight infants	To assess the effect of providing supplemental taurine for enterally or parenterally fed preterm or low birth weight infants on growth and development.	RCTs or quasi-RCTs	9/189
NR, not reported.				

Table 2  
Characteristic of interventions

Author	Feeding supplementation	Outcome improvement								Effectiveness of intervention
		Physical growth		Neurodevelopment		Biochemical outcomes	Other health outcomes	Morbidity of any disease	All-cause mortality	
		ST	LT	ST	LT					
Pammi et al.	Lactoferrin	NR	NR	NR	NSD	NR	Hospital stay ↓ <sup>c</sup> urinary tract infection ↓ <sup>c</sup>	LOS ↓ <sup>c</sup> Fungal sepsis ↓ <sup>b</sup>	NSD	Positive
Howlett et al.	Inositol	NR	NR	NR	NR	NR	NR	NSD	Neonatal death ↓ <sup>b</sup>	No impact
Walsh et al.	Iodine	NSD	NR	NR	NSD	NSD	NSD	NSD	NSD	No impact
Chi et al.	Prebiotics	NR	NR	NR	NR	NR	Days achieve full enteral feeding ↓ Hospital stay ↓ Stool frequency ↑	Sepsis ↓ ↓	↓	Positive
Armannia et al.	Prebiotics	NR	NR	NR	NR	NSD	Phototherapy rate ↓ <sup>c</sup> ; Hospital stay ↓ <sup>c</sup> ; Stool frequency ↑ <sup>a</sup>	Hyperbilirubinaemia ↓ <sup>c</sup>	NSD	Inconclusive
Amissah et al.	Fat	NSD	NR	NR	NR	NR	NSD	NR	NR	No impact
Amissah et al.	Protein	Weight ↑ <sup>c</sup> ; Length ↑ <sup>c</sup> ; HC ↑ <sup>c</sup>	NR	NR	NR	Blood urea nitrogen ↑ <sup>c</sup>	Hospital stay ↑ <sup>d</sup>	NSD	NR	Positive
Amissah et al.	Carbohydrate	Weight ↑ <sup>d</sup>	NR	NR	NR	NR	Hospital stay ↓ <sup>d</sup>	NSD	NR	Inconclusive

ST, Short term; LT, Long Term;

NR, Not reported; NSD, No statistical significance;

<sup>a</sup>, High certainty; <sup>b</sup>, Moderate certainty; <sup>c</sup>, low certainty; <sup>d</sup>, very low certainty;

↑, Increase; ↓, Decrease;

LCPUFA, long chain polyunsaturated fatty acid; HC, head circumference; LOS, late-onset sepsis; NEC, necrotizing enterocolitis.

Author	Feeding supplementation	Outcome improvement							Effectiveness of intervention	
		Length ↑; HC ↑.	NR	NR	NR	Ig-A ↑ Ig-G ↑	NR	NSD		NR
Yang et al.	Vitamin D									Positive
						IL-12 ↑				
Harding et al.	Calcium and/or phosphorus	NSD	NR	NR	NR	NSD	NSD	NR	NR	Inconclusive
Shah et al.	Arginine	NR	NSD	NR	NSD	NR	NR	NEC ↓ <sup>b</sup>	NSD (death related to NEC ↓ <sup>b</sup> )	Positive
Aceti et al.	Probiotic	NR	NR	NR	NR	NR	NR	LOS ↓ <sup>a</sup>	NR	Positive
Moe-Byrne et al.	glutamine	NSD	NR	NR	NSD	NR	Days achieve full enteral feeding ↓	NSD	NSD	No impact
Moon et al.	LCPUFA	Weight ↑ <sup>c</sup> ; Length ↑ <sup>c</sup> .	NSD	NR	NSD	NR	NR	NR	NR	No impact
AlFaleh et al.	Probiotics	NSD	NR	NR	NSD	NR	Hospital stay ↓; Days achieve full enteral feeding ↓	NEC ↓	↓	Positive
McCormick et al.	Mult-inutrient	HC ↑	Weight ↑; Length ↑; HC ↑	NR	NSD	NR	Bone mineral content (4/12 months) ↑	NR	NR	Inconclusive
Verner et al.	Taurine	NSD	NR	NSD	NR	NR	Intestinal fat absorption ↑	NSD	NSD	Inconclusive
ST, Short term; LT, Long Term;										
NR, Not reported; NSD, No statistical significance;										
<sup>a</sup> , High certainty; <sup>b</sup> , Moderate certainty; <sup>c</sup> , low certainty; <sup>d</sup> , very low certainty;										
↑, Increase; ↓, Decrease;										
LCPUFA, long chain polyunsaturated fatty acid; HC, head circumference; LOS, late-onset sepsis; NEC, necrotizing enterocolitis.										

## Quality assessment

The methodological quality of each SR was determined by the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool.(11) There are 11 items on the tool and each item accounts for 1 point. The total score is 11 which means the highest quality of SR. The downgraded total score was categorised into 3 groups: 0–3, 4–7, and 8–11 which represented low, medium, and high quality SRs.(12) Quality assessment was performed independently by two reviewers and any discrepancies would be discussed and resolved by inviting, if necessary, a third reviewer to make the final decision.

## Results

## Study selection

The initial search for all the potential SRs from the databases returned 1015 records, of which 861 remained after removing duplicates. Through title screening and abstract reading, 74 records were kept for full-text reading assessment. There were a further 57 articles excluded for the following reasons: (1) intervention did not meet the inclusion criteria; (2) topic duplication; and (3) there was no meta-analysis of the outcomes. Altogether, 17 eligible SRs met the inclusion criteria of this review. The study selection process is reflected in Fig. 1.

## Characteristic and quality assessment of included SRs

In total, 160 quantitative primary studies were synthesised in the 17 SRs, all of which were RCTs or quasi-RCTs. Nine SRs (3, 13–20) were published in the late 3 years (2018–2020), 5 SRs (21–25) were between year 2016 to year 2017 and only 3 SRs (26–28) were from year 2007, year 2010 and year 2014. Fourteen SRs (3, 13, 14, 16, 18–22, 24–28) were Cochrane SRs and 3 SRs (15, 17, 23) were conventional ones. As for the number of studies included, only 6 SRs (13, 15, 23–26) incorporated more than 10 primary studies with a relatively larger sample size. All the SRs assessed the effects of feeding extra nutrient supplementation to preterm infants by the improvement of their health. Considering the different health outcome assessments, some SRs (15, 16, 23, 26) focussed on the same interventions, and both were included to better observe the effect. Table 1 summarises the basic information of all the included SRs.

The results of the quality assessment using the AMSTAR tool are shown in Table 3. All the SRs were of high quality, with 2 SRs (13, 25) scoring 11, 9 SRs (3, 14, 16, 19, 21, 23, 24, 26, 28) scoring 10, 4 SRs (15, 18, 20, 27) scoring 9 and 2 SRs (17, 22) scoring 8. All the SRs met the AMSTAR criteria 1 (prior design provided), criteria 2 (duplicate study selection and data extraction), criteria 6 (characteristics of the included studies provided), criteria 7 (scientific quality of the included studies assessed and documented), and criteria 8 (scientific quality of the included studies used appropriately in formulating conclusions). The least met AMSTAR criteria was criteria 10 (likelihood of publication bias assessed) owing to the small number of the primary quantitative studies included in several SRs (3, 14, 16, 18–22, 27, 28).

Table 3  
Quality assessment of the included studies

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Pammi et al.	1	1	1	1	1	1	1	1	1	1	1	11
Howlett et al.	1	1	1	1	1	1	1	1	1	0	1	10
Walsh et al.	1	1	1	1	1	1	1	1	1	0	1	10
Chi et al.	1	1	1	0	0	1	1	1	1	1	1	9
Armannia et al.	1	1	1	1	1	1	1	1	1	0	1	10
Amissah et al.	1	1	1	1	1	1	1	1	0	0	1	9
Amissah et al.	1	1	1	1	1	1	1	1	1	0	1	10
Amissah et al.	1	1	1	1	1	1	1	1	0	0	1	9
Yang et al.	1	1	0	1	0	1	1	1	1	1	0	8
Harding et al.	1	1	1	1	1	1	1	1	0	0	0	8
Shah et al.	1	1	1	1	1	1	1	1	1	0	1	10
Aceti et al.	1	1	1	0	1	1	1	1	1	1	1	10
Moe-Byrne et al.	1	1	1	1	1	1	1	1	1	1	1	11
Moon et al.	1	1	1	1	1	1	1	1	1	0	1	10
AlFaleh et al.	1	1	1	1	1	1	1	1	1	0	1	10
McCormick et al.	1	1	1	1	1	1	1	1	0	0	1	9
Verner et al.	1	1	1	1	1	1	1	1	1	0	1	10

1 = Yes. 0 = No/ Unclear/ Not applicable. 1. Was an "a priori" design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Were potential conflicts of interest included?

## Characteristic of interventions

A total of 15 kinds of different nutrient supplementation for the feeding of preterm infants are summarised in this review (Table 2). The feeding supplementation can be classified into seven categories: protein (protein, lactoferrin), carbohydrate (prebiotic, inositol), fat (fat, LCPUFA), amino acid (arginine, glutamine), mineral (calcium), vitamin (vitamin D), and others (iodine, multi-nutrient, and probiotic).

## Effectiveness of the interventions on outcomes

Given that different outcomes were reported in each SR, the outcomes were classified into several groups displayed in Table 2. The outcomes which were of statistical significance, along with their quality – assessed by the Grades of Recommendation, Assessment, Development, and Evaluation guidelines (GRADE) – were both listed in Table 2.(29) No adverse effects of the feeding supplementation were reported in the included SRs, supporting the safety of the supplementation. With respect to the effectiveness of the interventions on the outcome improvement of preterm infants, the results and authors' conclusions of the included SRs were carefully checked, and were categorised into 3 groups: positive, no impact, and inconclusive.

### Positive

Seven SRs (13, 15, 17, 19, 21, 23, 26) concluded that there were positive effects to health improvement as a result of the extra supplementation in breast milk or formula. They were prebiotics, protein, arginine, vitamin D, and probiotics which were added to the feeding of preterm infants at a particular dose.

Pammi et al.(13) evaluated the effect of lactoferrin on the prevention of NEC and LOS. Twelve RCTs with 5425 participants were involved. The incidence of LOS was found to be decreased while that of NEC was not. In addition, duration of hospital stays and urinary tract infection rates were lower in the intervention group. All the synthesised evidence was graded as low quality apart from the rate of fungal sepsis.

Chi et al.(15) mainly focussed on the health improvement caused by prebiotic supplementation which was a kind of oligosaccharide and found to have impact on the probiotic bacteria in the intestinal tract.(15) Eighteen primary quantitative studies with 1322 participants were included. The meta-analysis showed that prebiotics could decrease the incidence of sepsis, mortality rate, duration of hospitalisation, time to reach full enteral feeding, and increase the stool frequency. The quality of the pooled results was not reported in the SR.

Aceti et al.(23) and AlFaleh et al.(26) both compared the effect of probiotic supplementation in preterm infants and had different health outcome assessments. Aceti et al.(23) aimed to evaluate whether type of feeding (exclusively human milk vs. exclusively formula or mixed feeding) affected the LOS prevention. The results confirmed the overall effect of probiotics in LOS prevention, but the subgroup analysis only found statistical significance in the exclusively human milk group. The quality of the evidence was high with 25 RCTs and 5868 participants involved. AlFaleh et al.(26) assessed multiple health outcomes although 11 primary studies were the same with Aceti et al.(23) Enteral probiotic supplementation was proved to reduce the incidence of severe NEC and mortality significantly, also, length of hospitalisation and days to reach full enteral feeding were shortened. Other health outcomes, such as short-term physical growth and neurodevelopment were found to have no statistical difference between groups. No quality assessment was applied in this SR.

Amissah et al.(19) reported the effect of protein supplementation on the feeding of preterm infants. Although it could promote physical growth in a short time, the extra protein increased the renal workload and extended the duration of hospitalisation. The results also needed to be interpreted cautiously with regard to the low to very low quality of evidence.

Shah et al.(21) assessed the effect of arginine supplementation on the incidence of NEC in preterm infants. NEC and its related mortality were both found to be decreased; these results were graded as being of moderate quality. No statistical difference was found in long-term physical growth and neurodevelopment.

Yang et al.(17) compared high dose (800–1000U/d), low dose (400U/d), and control groups of vitamin D supplementation. The results revealed better development (the length and head circumference) and immune function (IL-12, IgA, IgG) in the high dose group. The quality of evidence was not assessed in the SR.

### No impact

Five SRs (3, 14, 18, 24, 25) reported no impact of the interventions on the preterm infants. These supplements were inositol, iodine, fat, glutamine, and LCPUFA.

Walsh et al.(14) and Amissah et al.(18) concluded there was no impact of the iodine and fat supplementation owing to the outcome of no health improvement. Another 3 SRs (3, 24, 25) did not find any evidence supporting their major outcome improvements though some positive results were observed.

### Inconclusive

Five SRs (16, 20, 22, 27, 28) concluded that there was insufficient evidence to determine the effects of feeding supplementation on preterm infants of prebiotics (for prevention of hyperbilirubinaemia), carbohydrate, multi-nutrient, taurine, calcium, and phosphorus.

Armannia et al.(16) reported that the current evidence was unable to prove the effectiveness of prebiotics on hyperbilirubinemia prevention due to the low quality of evidence. Amissah et al.(20) only included 1 RCT with 75 participants in the SR. The preterm infants in the experimental group had increased weight and decreased duration of hospitalisation. Given the very low quality of evidence, negative results in morbidity, and small sample size, the SR fell short of being able to provide a conclusion by some distance. SRs conducted by Harding et al.(22), McCormick et al.(27) and Verner et al.(28) were also limited because of the reasons above.

## Discussion

Although medical technology has made great progress in recent years, prematurity is still a global health problem which requires a substantial financial investment in order to save lives.(30) Furthermore, surviving preterm infants suffer from a higher rate of morbidity and mortality, as well as delayed physical and neurological development compared with term infants.(30) Because of all these potential complications, multiple preventative strategies have been developed and examined, and feeding supplementation is one of the nutrition methods that can alleviate the situation.

This review of the feeding supplementation of preterm infants gives an overall insight into the assessment of the effectiveness of health improvement or disease prevention. In total, 15 kinds of nutrient supplementation were reported in the included SRs, but not all the supplements were confirmed to have a positive impact on the preterm infants with 5 SRs concluding there was no impact and 5 SRs whose results were inconclusive.

The interventions with positive effects reported in the SRs were: lactoferrin, prebiotic, probiotic, vitamin D, protein, and arginine. All the SRs were evaluated as being of high quality, with 5 SRs (13, 15, 22, 23, 26) including more than 10 RCTs which involved a relatively large number of participants, which guaranteed academic authority. Despite these advantages, implications or suggestions provided by the SRs included should not be ignored either.

Lactoferrin is the dominant protein in human milk and has been proved to perform a series of functions including a wide spectrum of anti-microbial effect, the immunomodulation of host defence, and the promotion of gut growth and maturation.(31) Though previous studies have confirmed the safety and effectiveness of the use of lactoferrin on humans, it is still hard to recommend it for clinical use in view of the publication bias and small studies of poor methodology expanding the effect size.(13) Probiotic refers to live strains of microorganisms while prebiotic refers to a nonviable food component.(32) Both of them could modulate the intestinal microbiota.(33) Chi et al.(15), Aceti et al.(23) and AlFaleh et al.(26) have reported the effect of prebiotics and probiotics supplementation on the health outcomes in the SRs respectively. The combination of probiotics and prebiotics might better exert synergetic effects in the intestinal microbiota management which could be a research point in the future. In another study, Amissah et al. (19) assessed the effect of protein supplementation on growth development, but the current evidence is still of low to very low quality and the evidence is lacking of long term benefits or harms. It has been proved that arginine was the essential amino acid for infants, and the occurrence of NEC was associated with the low level of circulating arginine(34) Although the SR conducted by Shah et al.(21) confirmed its effect in preventing NEC, a larger sample size and more research details focussed on the NEC stage 2 or 3 are still required. The daily intake of vitamin D for preterm infants recommended by the European Society of Paediatric Gastroenterology (ESPGAN) was 800–1000 IU/day.(35) The preterm infants in the high dose group (800–1000 IU/day) had better growth while the circulating concentrations of 25(OH)D, calcium, and phosphorus were found to have no statistical significance between the high dose group (800–1000 IU/day) and low dose group (400 IU/day).(17) Therefore, caution is still needed in adopting the optimal dose intake for preterm infants and we should not just follow the recommendations without consideration in case of the toxic effect.

The implications suggested by the SRs with 'no impact' and 'inconclusive' conclusions are also important. First, no further research priority should be given to inositol and iodine supplementation and the feeding of them to preterm infants. Second, some nutrient supplementation, such as fat, carbohydrate, calcium, and phosphorus might work as fortifying components of human milk, thus aiding the understanding of the nutritional requirements of preterm infants. Third, research on the supplementation of prebiotic (for prevention of hyperbilirubinaemia), taurine, glutamine and multi-nutrient could focus on the feeding details including the dose and duration. Next, more large and well-designed RCTs are needed to address the unsolved issues in the SRs. Last but not least, all feeding supplementation for preterm infants should respect their parents' choice, follow the ethical rules, and be proceeded with cautiously.

To the best of our knowledge, this is the first comprehensive overview of SRs focussing on feeding supplementation in preterm infants. The summary of the characteristics of the SRs and the interventions can help researchers become quickly familiar with trends in this area, which might stimulate new ideas among them. Most of the included SRs were from Cochrane; they were of the highest quality and will be updated every several years.(36) The strength of this review also lies in aspects including a systematic literature search, clear inclusion and exclusion criteria, standard data extraction, and a professional-quality assessment tool, making the results more robust and reliable.

Limitations of the review were also inevitable. Most of the SRs included did not report the long-term physical growth and neurodevelopment outcome assessment. The quality of the evidence in some SRs was low to very low, thus requiring more large and well-designed RCTs to raise quality. Although no language restriction was applied, all the included SRs were published in English which might have left some significant SRs uncaptured. The overlapping effect might also exist and we could not assess it due to the primary studies being included in more than one SR.(37)

## Abbreviations

SR: systematic review; AMSTAR: Assessing the Methodological Quality of Systematic Reviews; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analyses; GRADE: Grades of Recommendation, Assessment, Development, and Evaluation; ESPGAN: European Society of Paediatric Gastroenterology; NR: not reported; ST: Short term; LT Long Term; NSD: No statistical significance; LCPUFA: long chain polyunsaturated fatty acid; HC: head circumference; LOS: late-onset sepsis; NEC: necrotizing enterocolitis.

## Declarations

### Ethics approval and consent to participate

Not applicable

### Consent for publication

Not applicable.

## Availability of data and material

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

**Conflicts of interests** None declared.

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## Authors' contributions

Jiaxin Tao contributed to the acquisition of the data and draft the manuscript. Yanwei Su and Jing Mao contributed equally to define the research theme and be fully accountable for ensuring the integrity and accuracy of the work. Jixin Yang and Yanwei Su contributed to the analysis of the data and interpret the results. Yufeng Li contributed to critically revise the manuscript. All authors have read and approved the final manuscript.

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## Figures

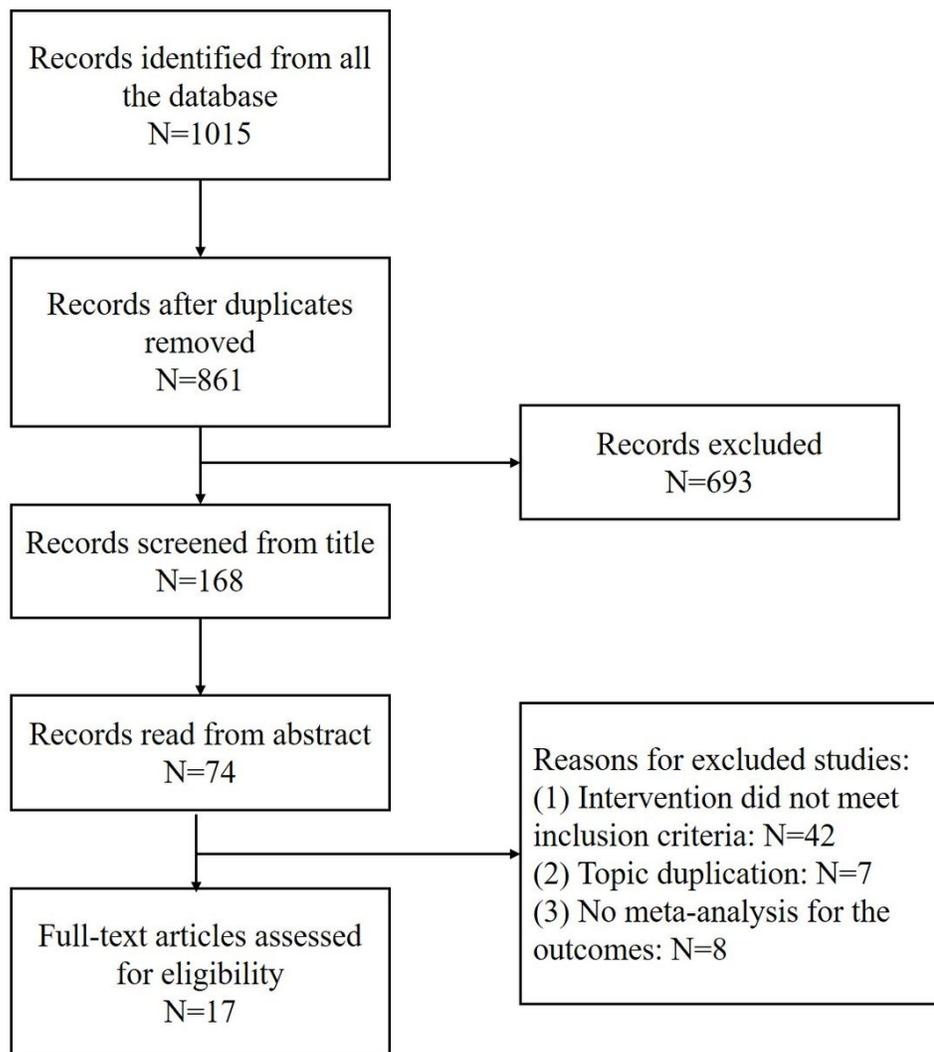


Figure 1

The flow diagram of study selection.