Clinical outcomes following pre-, pro- and synbiotic supplementation after caesarean birth or antibiotic exposure in the first week of life in term born infants: A systematic review of the literature

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Background: Caesarean section and early exposure to antibiotics disrupt the developing gastrointestinal microbiome, which is associated with long-term health effects.

Objective: The aim of this systematic review was to summarise the impact of prebiotics, probiotics, or synbiotics supplementation on clinical health outcomes of term infants born by caesarean section or exposed to antibiotics in the first week of life.

Design: A systematic search was performed in Medline and Embase from inception to August 2021. Title and abstract screening ($n = 11{,}248$), full text screening ($n = 48$), and quality assessment were performed independently by two researchers.

Results: Six RCTs studying caesarean born infants were included, group sizes varied between 32–193 with in total 752 children. No studies regarding supplementation after neonatal antibiotic exposure were found. Three studies administered a probiotic, one a prebiotic, one a synbiotic, and one study investigated a prebiotic and synbiotic. Several significant effects were reported at follow-up varying between 10 days and 13 years: a decrease in atopic diseases ($n = 2$ studies), higher immune response to tetanus and polio vaccinations ($n = 2$), lower response to influenza vaccination ($n = 1$), fewer infectious diseases ($n = 2$), and less infantile colic ($n = 1$), although results were inconsistent.

Conclusions: Supplementation of caesarean-born infants with prebiotics, probiotics, or synbiotics resulted in significant improvements in some health outcomes as well as vaccination responses. Due to the variety of studied products and the paucity of studies, no recommendations can be given yet on the routine application of prebiotics, probiotics, or synbiotics to improve health outcomes after caesarean section or neonatal antibiotic exposure.

Introduction

Early life is an important period as the infant's immune system is still developing (1). The development of the immune system is influenced by the gut microbiome (1), which develops rapidly after birth (2). Disruption of the developing gut microbiome (dysbiosis) due to environmental factors have been associated with adverse long-term health effects (3, 4).

Caesarean section (CS) is one of the main causes of aberrant microbiome development because it affects the diversity and colonization pattern of the gut microbiome (5–7). Due to reduced vertical mother-infant transmission of beneficial gut bacteria, the infant is predominantly colonized with bacteria from the skin, mouth and hospital environment (8–14). This is associated with an altered immune development, a higher risk of childhood obesity, atopy, allergy, asthma, and type 1 diabetes mellitus (10, 15, 16).

Another important cause of early-life dysbiosis is antibiotic exposure (17–19). Antibiotics are the most frequently prescribed drugs for neonates in their first week of life (20, 21), but their effects on later health outcomes have not yet been fully elucidated. So far, a few observational studies have shown that infants exposed to antibiotics in their first week of life had an altered gut microbiota (22–25) and it was associated with an increased risk of wheezing (26–28), infantile colic (26), gastrointestinal disorders (29) impaired growth (22, 30), allergies (31), allergic rhinitis (27), functional abdominal pain (32) and asthma (33, 34).

Potential interventions to reduce some of these long-term effects of early life dysbiosis include supplementation with prebiotics, probiotics, or synbiotics. Prebiotics are nutrients that promote growth and activity of beneficial bacteria that already exist in the gut (35), probiotics are live microorganisms such as Bifidobacteria and Lactobacilli (13), and synbiotics are a combination of pro- and prebiotics (36). The aim of this systematic review was to summarise the impact of prebiotics, probiotics, or synbiotics supplementation on clinical health outcomes of term infants born by caesarean section or exposed to antibiotics in the first week of life.

Methods

Literature search

This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (37). OVID Medline and Embase were systematically searched from inception to 3 August 2021. A multi stranded search approach comprised the following concept combinations:

([c section] OR ([antibiotic treatment] AND [first week of life] OR [first week antibiotics])) AND

- [pre- pro- synbiotics]
OR
- [dietary supplements] AND [microbiome]
OR
- [dietary supplements brands]

To reduce recall bias and enhance search results precision VOS-viewer was used to identify terms for NOTing out irrelevant records from databases searched (38, 39). No other filters or limits were used (Supplementary Appendix S1).

Inclusion criteria

(1) study participants were term-born infants (born between 37 and 42 weeks of gestation) and born via caesarean section or exposed to antibiotics in the first week of life; (2) exposure to pre-, pro- or synbiotic dietary supplements administered within six weeks after birth; (3) clinical outcomes were reported; (4) study design was a randomised controlled trial (RCT).

Exclusion criteria

(1) including infants with major congenital malformations; (2) written in a language other than English; (3) animal studies; (4) for the caesarean-analyses: if a study includes both vaginally and caesarean-delivered infants and there were no subgroup analyses for only the caesarean-delivered infants

Data collection

After the search, all records were imported into Rayyan after deduplication (40). Two researchers (NC and KK) independently performed title and abstract screening, as well as full-text screening. After consensus about the included articles, relevant data were extracted by NC in consultation with the other co-authors. Odds ratios (ORs), 95% confidence intervals (95% CI) and P-values were included in the table if these were provided in the original articles. If both "per protocol" and "(modified) intention to treat" analyses were available, only the results from the "(modified) intention to treat" analysis were included.

Critical appraisal

To assess the risk of bias in the included articles, the Cochrane risk-of-bias tool for randomised controlled trials (RoB 2) (41) was used. The RoB 2 assesses the risk of bias in the studies in five domains (**Table 1**). The risk of bias was independently assessed by two researchers (NC and KK) and any discrepancies were discussed until a consensus was reached.

Data analyses

Due to the heterogeneity in the interventions and outcomes evaluated in this systematic review, it is not possible to synthesize data from these studies in a meta-analysis. Therefore, a descriptive synthesis of the data was performed.

Results

Of the 14,632 records, 11,248 remained after removing duplicates. After title and abstract screening, 55 articles were read in full-text, and eight articles were included for analysis (see **Figure 1**).

Study characteristics

Eight articles were included, based on six RCTs (**Figure 1**), with a total of 752 children. Most studies scored a high risk of bias (**Table 1**). The characteristics of the included studies are summarised in **Table 2**. In all studies, supplementation was administrated to infants born by CS; no studies were found after antibiotics in the first week of life. The antibiotic policy for CS was not described in most studies, only Chua et al. (42) stated that infants born via CS were exposed to intrapartum antibiotics prophylaxis. It is likely that in more studies caesarean-born infants were exposed to antibiotics in utero.

In three articles, based on the same study, the intervention was a probiotic mixture (43–45) [see **Table 2**]. In two other studies, the intervention group was also given a probiotic (46, 47) and the interventions of the other three studies were prebiotics (48), synbiotics (49), and either pre- or synbiotics (42). All interventions were started within two weeks after birth, except for one study in which the intervention was started at six weeks of age (47). The intervention was administered for six months in most studies, except for two studies in which the intervention was continued until 12 weeks of age (47) or 16 weeks of age (42). In five RCT's, the intervention group was only compared with the placebo control group and not with the breastfed reference group for

the clinical outcomes. Therefore, only the results between the intervention and the control groups are reported.

Atopic diseases

Four articles examined the effect of supplementation on atopy. Three articles (43–45) based on the same RCT evaluated the effect of a prenatally started probiotic supplement until six months of age on allergic disease in infants ($n = 146$) at risk for atopic diseases at 5, 10 and 13 years of age. There was no significant difference between the intervention and control group for most outcomes regarding eczema, sensitisation, any allergic disease, and rhinitis until 13 years of follow-up (**Table 3**). The reported significant results were a decrease in IgE-associated eczema, and a positive (food) skin prick test (SPT) response and/or food-specific IgE >0.7 kU/L at 0–5 years of age in the intervention group (44). At 13 years of age, there was a significant decrease in eczema and any allergic disease experienced in the last 12 months, based on the ISAAC questionnaire (43, 50). The study by Chua et al. (42) examined the effect of a prebiotic and a synbiotic supplementation administrated until 16 weeks of age ($n = 153$). In post-hoc analyses, fewer skin disorders and atopic dermatitis/eczema were found in the synbiotic group, but not in the prebiotic group compared to the control group at 22 weeks.

Infectious diseases

Two studies (45, 48) examined the effects of prebiotic (48) or synbiotic (45) supplementation in the first six months of life on infectious diseases. Puccio et al. found that infants ($n = 64$) in the prebiotic intervention group had a lower risk of lower respiratory infection at 6 months OR 0.17 (95% CI, 0.02–0.96), or 12 months OR 0.21 (95% CI, 0.04–0.83) or bronchitis at 12 months OR 0.06 (95% CI, 0.00–0.50) than those in the control group (48). Peldan et al. found after 5–10 years follow-up ($n = 144$) that the probiotic intervention was associated with a reduced risk of receiving antibiotics over the past five years OR 3.19 (95% CI, 1.02–9.97) and a lower risk of having four or more upper respiratory infections in one year 0.29 (95% CI, 0.12–0.72) (45).

Gastrointestinal effects

Three articles assessed the effect of a prebiotic (48), probiotic (46), and a synbiotic (49) supplementation in the first six months of life on diarrhea (46), stool pattern (49) and colic (48) in the first year of life. Cooper et al. found up to 6 months of age, more liquid stools and fewer formed and hard stools were reported in the probiotic group compared to the control group ($n = 193$) (49). Baglatzi et al. ($n = 164$) found no differences in diarrhoea during the first year (46). Puccio et al. ($n = 64$) found a significantly lower incidence of parent-reported infantile colic at four months of age in the

TABLE 1 Risk of bias of the included studies.

First author	Domains of the Cochrane risk-of-bias tool for randomised controlled trials (RoB-2)					
	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Total
Puccio (48)	Green	Green	Green	Red	Red	Red
Chua (42)	Yellow	Red	Red	Green	Green	Red
Kallio (43)	Green	Green	Red	Yellow	Yellow	Red
Kuitunen (44)	Green	Green	Green	Green	Green	Green
Peldan (45)	Green	Green	Red	Red	Green	Red
Baglatzi (46)	Green	Red	Green	Green	Green	Red
Cooper (49)	Green	Red	Green	Red	Green	Red
Holscher (47)	Yellow	Green	Green	Green	Green	Yellow

Domain 1: Risk of bias arising from the randomisation process.
Domain 2: Risk of bias due to deviations from the intended interventions (*effect of adhering to intervention*).
Domain 3: Missing outcome data.
Domain 4: Risk of bias in measurement of the outcome.
Domain 5: Risk of bias in selection of the reported result.
Green: low risk of bias, yellow: some risk of bias, red: high risk of bias.
If a study included both vaginally and caesarean-delivered infants and a subgroup analysis on the caesarean-delivered infants was performed, only the methods used for this relevant subgroup analyses were assessed.
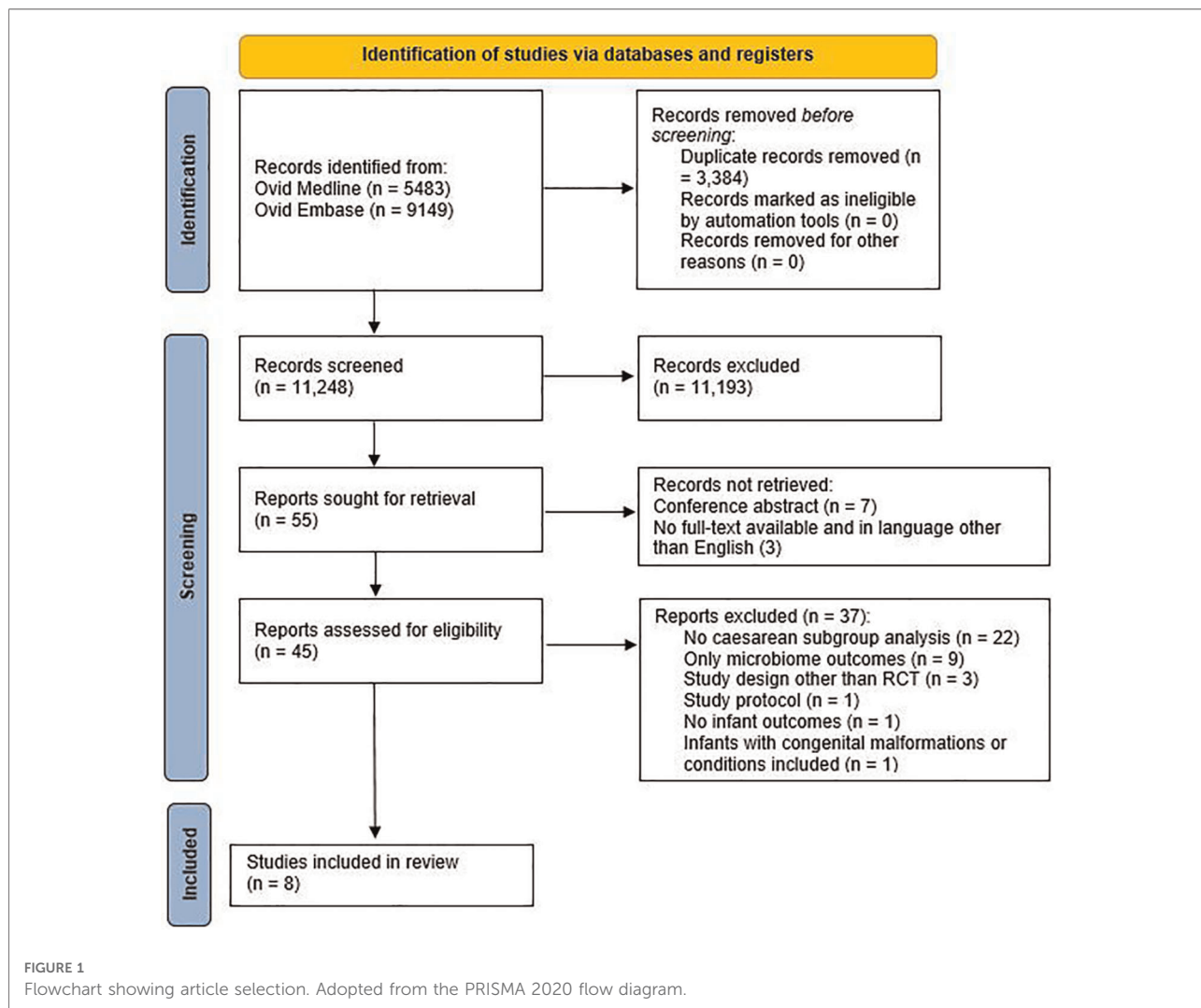

FIGURE 1
Flowchart showing article selection. Adopted from the PRISMA 2020 flow diagram.

TABLE 2 General characteristics of the included studies.

First author	Country	Study period (year published)	# Participants[a]			AB or CS SG?	Intervention	Control	Start of intervention	Duration intervention	Outcomes (relevant subgroup)	Follow-up	Comments
			I	C	T								
Puccio (48)	Italy & Belgium	2012–2015 (2017)	32	32	64	CS SG	Prebiotics: 2 HMOs (2′-fucosyllactose and lacto-N-neotetraose)	Control formula	0–14 D	6 M	Colic, nighttime awakenings, bronchitis, LRTI	1, 2, 3, 4, 6, 12 M	Safety study, CS SG results are only reported if they are significant
Chua (42)	Singapore & Thailand	2011–2013 (2017)	52 + 51	50	153	CS	Prebiotic (scGOS/lcFOS) or synbiotic (scGOS/lCFOS and Bifidobacterium breve M-16 V)	Control formula	1–3 D	16 W	**Total faecal Bifidobacteria, Bifidobacterium species** abundance, other members of the gut microbiota, pH, sc fatty acids, lactate, atopic dermatitis/eczema	3, 5 D 2, 4, 8, 12, 16, 22 W	Infants born via CS were also exposed to intrapartum AB prophylaxis[b].
Kuitunen (44)	Finland	2000–2003 (2009)	70	76	146	CS SG	Probiotic: Lactobacillus rhamnosus LC705, Bifidobacterium breve Bb99, Propionibacterium freudenreichii spp., shermanii JS	Placebo (micro-crystalline cellulose)	36 W gestation + from birth	6 M	**(IgE-mediated) allergic disease,** eczema, food allergy, asthma, allergic rhinitis, IgE sensitisation alone	5 Y	Infants were at risk for atopic diseases (at least one parent with asthma, allergic rhinitis or eczema). The intervention was initiated prenatally (36 W gestation)
Peldan (45)	Finland	2000–2003 (2017)	69	75	144						**Allergic disease, eczema, allergic rhinitis, asthma,** URTIs, LRTIs, AB use, food allergy	10 Y	Kallio et al.: significant differences between sub- and main group: longer BF, older maternal age in CS SG, more use of prebiotics after 13 years in intervention group Peldan et al.: more use of probiotics after the study period in the intervention group
Kallio (43)	Finland	2000–2003 (2019)	53	56	109						Allergic disease (**doctor-diagnosed,** ISAAC), **sensitisation**	13 Y	
Baglatzi (46)	Greece	2009–2011 (2016)	84	80	164	CS	Probiotic: regular dose of Bifidobacterium lactis	Low dose of B. lactis	Birth	6 M	**Diarrhoea,** immune and gut maturation, microbiota, immune response to vaccines, anthropometry	12 M	No control group that was fed formula without pre/pro/synbiotics
Cooper (49)	South Africa	2008–2013 (2016)	92	101	193	CS SG	Synbiotic: BMOs (containing GOS and MOS such as 3′- and 6′ sialyllactose) + Bifidobacterium lactis CNCM-I-3446	Control formula	Birth (≤3 D)	6 M	Faecal (**bifido)bacteria, anthropometrics,** faecal pH, lean mass, fat mass and bone mineral content, digestive tolerance, immune parameters, HIV infection	1 Y	The included infants all have HIV+ mothers and all mothers and infants received antiretroviral medication. Infants

(continued)

TABLE 2 Continued

First author	Country	Study period (year published)	# Participants[a]			AB or CS SG?	Intervention	Control	Start of intervention	Duration intervention	Outcomes (relevant subgroup)	Follow-up	Comments
			I	C	T								
											status, frequency of morbidity episodes		who tested positive for HIV were excluded
Holscher (47)	USA	2007–2008 (2012)	16	16	32	CS SG	Probiotic: *Bifidobacterium animalis* subspecies lactis (Bb12)	Control formula	6 W	12 W	**Faecal sIgA**, anti-rotavirus-specific IgA, faecal anti-poliovirus-specific IgA	12 W	

CS, Caesarean section; SG, subgroup; I, intervention; C, controls; T, total; BF, breastfeeding; FF, formula feeding; HMOs, human milk oligosaccharides; (sc) GOS, (short chain) galactooligosaccharides; (lc) FOS, (long chain) fructooligosaccharides; Spp, several species; BMOs, bovine milk oligosaccharides; MOS, milk oligosaccharides; D, days; M, months; W, weeks; H, hours; Y, year; AB, antibiotic; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection; ISAAC, International study of asthma and allergies in childhood; HIV, human immunodeficiency virus; sIgA, secretory Immunoglobulin A.

Outcome in **bold** was the primary outcome of the study.

[a] # participants in a subgroup, if applicable.

[b] The antibiotic policy for CS was not described in most studies, only Chua et al. (42) stated that infants born *via* CS were exposed to intrapartum antibiotics prophylaxis. It is likely that in more studies caesarean-born infants were exposed to antibiotics *in utero*.

TABLE 3 Clinical outcomes.

First author	Intervention			Participants[a]			Outcome	Significant outcomes				Non-significant outcomes	Comments
	Type	Start	Duration	I	C	T		Reply/specific outcome	Time point	OR (95% CI)	P-value		
Allergic disease													
Chua (42)	Prebiotic (scGOS/lcFOS)	1–3 D	16 W	52	50	102	–	–	22 W	–	–	1. 1.All skin disorders at 22 W 2. 2.Atopic dermatitis/eczema at 22W	Post-hoc analysis
	Synbiotic (scGOS/lcFOS and *B. breve* M-16 V)	1–3 D	16 W	51	50	101	Skin disorders	All skin disorders / Atopic dermatitis/eczema	22 W / 22 W	– / –	0.017 / 0.037	–	
Kuitunen (44)				70	76	146	Allergic disease	**Positive SPT response**	0–5 Y	0.47 (0.23–0.96)	<0.05	1. 1.**Allergic disease: positive SPT response at 0–2 Y, specific IgE >0.7 kU/L at 0–5 Y** 2. 2.Sensitization: positive SPT response and/or specific IgE >0.7 kU/L at 0–2 and 0–5 Y 3. 3.Allergic disease: all eczema at 0–2 and 0–5 Y, IgE-associated eczema at 0–2 Y, IgE-associated asthma and rhinitis at 0–2 and 0–5 Y	–
								Eczema: IgE-associated	0–5 Y	0.43 (0.19–0.95)	<0.05		
							Sensitisation	Positive food SPT response and/or food-specific IgE >0.7 kU/L	0–5 Y	0.33 (0.12–0.85)	<0.05		
Peldan (45)	Probiotic: *L. rhamnosus* LC705, *B. breve* Bb99, *P. freudenreichii* spp., *shermanii* JS	36 W gestation + from birth	6 M	69	75	144	–	–	–	–	–	1. 1.Any allergic disease ever: ISAAC, doctor-diagnosed, ISAAC at 5–10 Y 2. 2.Eczema ever: ISAAC, doctor-diagnosed, ISAAC at 5–10 Y 3. 3.Allergic rhinitis ever and in the last 5–10Y: ISAAC, doctor-diagnosed 4. 4.Asthma ever: ISAAC, doctor-diagnosed, ISAAC at 5–10 Y 5. 5.Doctor-diagnosed food allergy ever	Allergic rhinitis was significantly decreased in the intervention group in the unadjusted OR

(continued)

TABLE 3 Continued

First author	Intervention			Participants[a]			Significant outcomes					Non-significant outcomes	Comments
	Type	Start	Duration	I	C	T	Outcome	Reply/specific outcome	Time point	OR (95% CI)	P-value		
Kallio (43)				53	56	109	Allergic disease (ISAAC, last 12 M)	Allergic disease	13 Y	0.336 (0.154–0.736)	0.006	1. **1.Allergic disease: any/ specific IgE >0.7 kU/L** 2. 2.Sensitization: any/food-specific/inhalant-specific IgE >0.7/>0.35 kU/L 3. 3.Doctor-diagnosed allergy ever: all/IgE-associated eczema, asthma, rhinitis or food allergy 4. 4.ISAAC-diagnosed allergic disease in last 12 M: allergic disease, specific IgE >0.7 kU/L, IgE-associated eczema, asthma and rhinitis	Holm method was used to adjust for multiple comparisons
								Eczema		0.388 (0.162–0.930)	0.031		
Infectious diseases													
Puccio (48)	Prebiotics: 2 HMOs (2'-fucosyllactose and lacto-N-neotetraose)	0–14 D	6 M	32	32	64	LRTI	Any	6 M	0.17 (0.02–0.96)	0.043	–	Unclear if other analyses were performed
								Any	12 M	0.21 (0.04–0.83)	0.022		
							Bronchitis	Any	12 M	0.06 (0.00–0.50)	0.003		
Peldan (45)	Synbiotic: L. rhamnosus LC705, B. breve Bb99, P. freudenreichii spp., shermanii JS and GOS	36 W gestation + from birth	6 M	69	75	144	No AB	During last 5 years	5–10 Y	3.19 (1.02–9.97)	0.046	1. LRTI, ≥1/5 years	ORs are adjusted ORs
							URTI	≥4/year	5–10 Y	0.29 (0.12–0.72)	0.004		
Gastrointestinal effects													
Baglatzi (46)	Probiotic: regular dose of B. lactis (vs. low dose)	Birth	6 M	84	80	164	–	–	1 Y	–	–	1. **Diarrhoea: prevalence, incidence and number of days of diarrhoea at 1 Y**	high dose considered intervention, low

(continued)

TABLE 3 Continued

First author	Intervention			Participants[a]			Outcome	Significant outcomes				Non-significant outcomes	Comments
	Type	Start	Duration	I	C	T		Reply/specific outcome	Time point	OR (95% CI)	P-value		
													dose considered control
Cooper (49)	Synbiotic: BMOs (containing GOS and MOS such as 3'- and 6' sialyllactose) + B. lactis CNCM-I-3446	Birth (≤3 D)	6 M	92	101	193	Stool consistency	↑ Liquid / ↓ Proportion of days in which hard stool was reported (mean %) / ↓ Proportion of days with formed stools	10 D, 4 W, 6 W, 3 M, 4 M, 6 M	– / – / –	<0.001 / 0.001 / 0.045	1. 1.Frequency of daily stools at 3 D, 10 D, 28 D and 3 M 2. 2.Frequencies of flatulence, spitting up, vomiting, crying, fussing, or colic at 10 D, 28 D, 6 W, 3 M and 4 M	–
Puccio (48)	Prebiotics: 2 HMOs (2'-fucosyllactose and lacto-N-neotetraose)	0–14 D	6 M	32	32	64	Colic	↓ Colic reported	4 M	–	0.035	–	Unclear if other analyses were performed
Anthropometrics													
Baglatzi (46)	Probiotic: regular dose of B. lactis (vs. low dose)	Birth	6 M	84	80	164	–		1 M, 4 M, 12 M	–	–	1. Weight-for-age, length-for-age, BMI-for-age and head-circumference-for-age at 1 M, 4 M and 12 M	high dose considered intervention, low dose considered control
Cooper (49)	Synbiotic: BMOs (containing GOS and MOS such as 3'- and 6' sialyllactose) + B. lactis CNCM-I-3446	Birth (≤3 D)	6 M	92	101	193	Daily weight gain	Between 10 D and 4 M (mean)	4 M	–	0.010 (Non-inferiority P-value)	1. 1.Weight-for-age, length-for-age, BMI-for-age and head-circumference-for-age at 10 D, 4 W, 6 W, 3 M, 4 M and 6 M 2. 2.Fat mass and percentage mean fat mass at 4 M and 12 M	Body weight was adjusted for baseline value and sex Non-inferiority analysis
Behaviour													
Puccio (48)	Prebiotics: 2 HMOs (2'-fucosyllactose and lacto-N-neotetraose)	0–14 D	6 M	32	32	64	Nighttime awakenings	→	2 M	–	0.036	–	Unclear if other analyses were performed
Vaccination response													
Baglatzi (46)	Probiotic: regular dose of B. lactis (vs. low dose)	Birth	6 M	84	80	164	Immune responses to vaccinations	↑ Response to Tetanus [IU/ml, median (n; 25th–75th percentile)]	12 M	–	0.0411	1. Immune responses to vaccination at 7 M and 1 Y: diphteria, B. pertussis, tetanus, polio, infants who reached	high dose considered intervention, low

(continued)

TABLE 3 Continued

First author	Intervention			Participants[a]			Significant outcomes						Non-significant outcomes	Comments
	Type	Start	Duration	I	C	T	Outcome	Reply/specific outcome	Time point	OR (95% CI)	P-value			
								↓ Response to H. influenza B [μg/ml, median (n; 25th–75th percentile)]		–	0.0186		anti-HiB protective antibody over the 12 M	dose considered control
Cooper (49)	Synbiotic: BMOs (containing GOS and MOS such as 3'- and 6' sialyllactose) + B. lactis CNCM-I-3446	Birth (≤3 D)	6 M	92	101	193	–	–	6 W, 4 M, 12 M	–			1. Immune measurements: positive anti-hepatitis B IgG antibody response	–
Holscher (47)	Probiotic: B. animalis subspecies lactis (Bb12)	6 W	12 W	16	16	32	Immune responses to vaccinations	↑ anti-polio-specific IgA (U/g) after vaccination	12 W compared to 8 W	–		0.026	1. Change in anti-rotavirus-specific IgA after vaccination between 8 W and 12 W	–

I, intervention; C, controls; T, total; CS, Caesarean section; SG, subgroup; OR, odds ratio; HMOs, human milk oligosaccharides; BMOs, bovine milk oligosaccharides; MOS, milk oligosaccharides; SPT, skin prick test; ISAAC, International study of asthma and allergies in childhood; D, days; M, months; W, weeks; H, hours; Y, year; AB, antibiotic; LRTI, lower respiratory tract infection; URTI, upper respiratory tract infection.

intervention group, which was collected in a diary with the options "never," "sometimes," and "often".

Anthropometrics

Two studies (46, 49) examined the effect of a probiotic (n = 164) (46) and synbiotic (49) supplement (n = 193) on anthropometric measurements during the first year of life. Both studies found no differences in anthropometric measurements including weight-for-age, length-for-age, BMI-for-age, head-circumference-for-age and fat mass between intervention and control group infants (46, 49).

Behaviour

Puccio et al. (48) found significantly fewer parent-reported night time awakenings at 2 months in the prebiotic group compared to the placebo group (n = 64) (48). Parents reported these awakenings as "never," "sometimes," and "often". The difference did not persist after two months of age.

Immune response

Three studies (46, 47, 49) investigated the effect of a probiotic (46, 47) or a synbiotic (49) supplement on the infants' immune system. Holscher et al. (47) found after probiotic supplementation between six and twelve weeks of age a significantly higher increase in anti-polio-specific IgA after vaccination at 12 weeks compared to 8 weeks (n = 32). Baglatzi et al. (46) found after six months of probiotic supplementation a significantly higher immune response to tetanus vaccinations (n = 164), but a lower immune response to H. influenza B vaccinations at 12 months for the regular dose group compared to the low dose group. In contrast to Holscher at al. (47), no significant differences in immune response to polio vaccinations was found (46). Cooper et al. (49) found no significant differences after synbiotic supplementation (n = 193).

Safety

All the included studied reported safety in terms of growth and gastrointestinal tolerance and none noted significant differences in these parameters or in the number of adverse events between the intervention and the control group.

Discussion

This systematic review on the clinical effects of pre-, pro- or synbiotic supplementation after CS or antibiotic exposure in the first week of life shows several significant differences in clinical outcomes. The reported effects consisted of a decrease in atopic diseases, fewer infectious diseases, and difference in immune response to vaccinations. The results with regard to immune response to vaccinations were however inconsistent and only shown in CS born children. No studies were found regarding

the effects of pre-, pro- or synbiotics supplementation on clinical outcomes after neonatal antibiotic treatment.

Only one RCT was included in this review in which allergy was the primary outcome (44). It showed some promising results of probiotics for CS born children in a post-hoc analysis, but not for vaginally born children (43, 44). Both this RCT and the study of Chua et al. (42) showed that caesarean-born children in the intervention group had less eczema. The mechanisms behind the prevention of eczema following probiotics stem from the hygiene hypothesis, where early exposure to gut microbes directs the immune system away from a Th-2 skew (51) or upregulates Tk1-cytokine production (52). The protective effects of prebiotics may be by promoting bacterial growth of by immunomodulatory effects (52). Eczema in early life is an important risk factor itself for later allergy development (53), probably due to epicutaneous sensitization. We hypothesize that if pre-, pro- or synbiotic administration reduce the incidence of eczema, these children may have less atopic diseases later in life. Adequately powered studies on the effect of probiotic supplementation in children born following CS are needed to confirm this hypothesis.

Two other included studies in this systematic review support the results that supplementation promotes the development of a healthier immune system in caesarean-born infants. Both studies found fewer infectious diseases in the caesarean-born intervention group (45, 48). These studies also showed that the differences between the intervention and control groups persisted even after the intervention period. The potential immune modulation of the intervention can be long lasting; meaning that early supplementation can support the immune system to protect against later infectious diseases as found by Peldan et al. (45) after 5–10 years of follow-up. As the follow-up of one year in the study of Puccio et al. (48) was however relatively short, more studies with longer follow up are required to confirm these promising results.

Two of the three studies on immune response to vaccinations after probiotic supplementation found significant effects (46, 47). The immune response to vaccination is a valuable marker reflecting the development of the responsiveness of the immune system to foreign antigens (54, 55). These immunological benefits may be due to an enriched Bifidobacterium population in the gut microbiome. In the literature, an association has been found between reduced abundance of Bifidobacterial species and immune disorders such as pathogenic infections, and allergies (56, 57). Furthermore, an aberrant gut microbiome development has been observed in preterm infants, infants born by CS and after antibiotic exposure in early life, which are all characterized by reduced abundance of Bifidobacterium species (58, 59). Supplementation of a Bifidobacterium probiotic in caesarean-born infants may therefore contribute to a shift in the gut microbiome towards that of vaginally

delivered infants, resulting in immunological benefits. However, more studies on the effect of probiotics are needed.

One of the strengths of this review is that, to our knowledge, this is the first review examining the clinical effects of pre-, pro- and synbiotics rather than microbiome differences whose clinical effect is still unclear in caesarean-born infants or infants exposed to antibiotics in the first week of life. One systematic review has recently been published about the effects of probiotics, prebiotics and synbiotics on the microbiome of children born *via* CS (60). However, no clinical outcome measures were reported in this review, which is the ultimate goal for optimizing health in children born following CS or after antibiotic exposure in the first week of life. Furthermore, all full-texts were studied to see if any subgroup analyses of caesarean-born infants were performed, even if this was not explicitly stated in the title or abstract. As a result, only articles that performed analyses on caesarean-born infants were included, and not articles that only analysed the total group of participants, including vaginally born infants.

The main limitation of this review is that nearly all studies were not powered for the clinical outcomes. In most studies, the outcomes for the caesarean-born infants resulted from a subgroup analysis. Moreover, many articles did not adjust for multiple testing, which may have resulted in false positive results. In addition, six of the eight studies scored a high risk of bias, and the included studies were very heterogeneous with regard to the type of supplement studied, the start and duration of the supplementation and the outcome measures. It was therefore not possible to perform a meta-analysis. Furthermore, in the included studies the intervention groups were compared with control groups who received a placebo and, except for one study, not with a "gold standard": the reference groups of vaginally born and/or breastfed infants that were included in some of the articles. Finally, the follow-up durations of most studies were only one year or less and are therefore too short to investigate the long-term effects.

For future research, several recommendations can be made. Studies need to be adequately powered on clinical outcome measures to investigate the effect of the supplementation. The clinical outcomes of interest, where changes could be expected based on the literature, are: infections, type 1 diabetes, obesity, and atopic diseases such as eczema, allergy, and asthma. These outcome measures need adequate follow-up time. More studies with the same supplement are needed in order to advocate a specific supplement.

Conclusion

Supplementation of pre-, pro or synbiotics to infants delivered by caesarean section may result in significant improvements in various health outcomes. However, the results were sometimes contradictory or only found in a

limited number of studies, and most studies were not adequately powered for the clinical outcome measures. Currently, no studies have been performed examining the effect of supplementation after antibiotic exposure in the first week of life. Due to the variety of study products and the lack of studies, to date no recommendations can be made on how to influence the gut microbiome to improve health outcomes in infants born by caesarean section or with antibiotic exposure in the first week of their life.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

KK contributed to the design, the analysis and interpretation of the study, drafting of the initial manuscript, and reviewed and revised the manuscript. NC contributed to the design, analysis and interpretation of the study and critically revised the manuscript. AV and RvE contributed to the conception of the study, interpretation of the data and critically revised the manuscript. JD conceptualized and performed the systematic search and critically revised the manuscript. TdM contributed to the conception of the study, the interpretation of the data and critically revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.974608/full#supplementary-material.

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