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REVIEW

Stool characteristics of infants receiving short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides: A review

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Abstract

Human milk is considered to be the optimal source of infant nutrition. Some of the benefits of breastfeeding have been ascribed to human milk oligosaccharides (HMO). For instance, HMO can affect faecal characteristics such as stool consistency and stool frequency. Such effects on stool characteristics can be beneficial for young infants as hard stools and even constipation is common in that age group. Prebiotics in infant milk formulas have been introduced to exert similar functionalities. A specific mixture of prebiotics consists of a combination of short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides (scGOS/lcFOS) in a ratio of 9:1. This specific mixture has been developed to closely resemble the molecular size composition of HMO. Many studies have been done with scGOS/lcFOS, and indicators for digestive comfort have often been included as secondary outcomes. This review summarizes the effects of scGOS/lcFOS (9:1) on stool consistency, stool frequency and transit time in healthy term and preterm infants. In several of the studies with scGOS/lcFOS in a ratio of 9:1 in infant milk formulas, positive effects of this mixture on stool characteristics such as stool consistency and stool frequency were observed. As stool consistency was shown to be correlated to whole gut transit time, scGOS/lcFOS can be hypothesised to have a role in reducing the risk of constipation.

Key words: Short-chain galactooligosaccharides; Long-chain fructooligosaccharides; Stool consistency; Stool frequency; Infants

Core tip: In several clinical trials with a specific mixture of short-chain galacto-oligosaccharides and long-chain fructooligosaccharides in a ratio 9:1 in infant milk formulas, positive effects were observed on stool consistency and stool frequency. This specific mixture of short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides may therefore have a role in reducing the risk of constipation.

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STOOL CHARACTERISTICS AND CONSTIPATION IN INFANCY AND CHILDHOOD

Childhood constipation is a common problem, with a

prevalence ranging from 0.7% to 29.6%[1]. It is mentioned to be the main reason for a paediatric outpatient visit in 3% of all cases[2] and for 30% of the visits to paediatric gastroenterologists[3,4]. Symptoms of constipation start to occur during the first year of life in about 40% of children with functional constipation[5], In the past, infants on standard infant formula have been reported to suffer from hard, infrequent stools and even from constipation more often than infants receiving human milk[6-8]. This difference has partly been ascribed to human milk oligosaccharides (HMO), which are present in human milk in levels of approximately 1 g/100 mL[9].

EFFECTS OF HMO ON STOOL CHARACTERISTICS

HMO are prebiotic oligosaccharides[10], which are not hydrolysed by digestive enzymes in the small intestine[11,12]. In the colon, undigested substrates can be used by colonic bacteria: the intestinal microbiota. The intestinal microbiota is dependent on the provision of substrates for their growth. For instance, non-digestible carbohydrates such as dietary fiber and dietary oligosaccharides that reach the colon intact can stimulate the growth of colonic bacteria, resulting in an increase in bacterial mass. HMO is non-digestible oligosaccharides that reach the colon intact, and can be used as substrate for the intestinal microbiota[12-14]. As bacteria in the colon have a preference for specific types of substrates, the provision of a specific type of substrate in the form of HMO will result in selective fermentation by intestinal bacteria, which can change the composition of the intestinal microbiota. In this case, fermentation of the non-digestible carbohydrates from human milk is associated with selective growth of Lactobacillus species and Bifidobacteria[12,15]. As end-products of fermentation, lactate and short-chain fatty acids (SCFA), such as acetate, propionate and butyrate are produced. Lactate and SCFA can then be absorbed and used as an energy source for the host, but within the colon, SCFA have also been shown to have specific effects, such as being an energy source for the colonic mucosa, to have trophic effects on the intestinal mucosa, to stimulate mucosal blood flow and oxygen uptake and to affect sodium and water absorption [16]. Furthermore, human milk oligosaccharides have been suggested to increase mineral absorption[17,18].

As mentioned before, stool characteristics of infants who recieved human milk have in the past been reported to differ from infants on standard infant formula[6-8]. This difference has partly been ascribed to HMO. Several mechanisms can explain these effects. First, an increase in microbial mass due to the fermentation of the oligosaccharides can increase the faecal water content, which can results in softer stools. Second, the selective fermentation and growth of Lactobacillus species and bifidobacteria[19,20] and the subsequent production of SCFA can increase the water content of the faecal mass , but SCFA may also stimulate gastrointestinal motility, either by being used as energy source for colonic epithelial cells, or by inducing phasic and tonic contractions in circular muscle[21-25]. Third, as HMO are specific types of dietary fiber, they can be hypothesized to bind water and thereby increase the water content of the faecal mass[22].

EFFECTS OF SCGOS/LCFOS ON STOOL CHARACTERISTICS

In the last decade, several types and mixtures of non-digestible oligosaccharides have been used in infant formulas, such as galacto-oligosaccharides, fructo-oligosaccharides, polydextrose, and pectin hydrolysates. Although the compositional complexity of HMO cannot be mimicked completely today, a specific mixture of 90% short-chain galacto-oligosaccharides (derived from lactose, degree of polymerization 3-8) and 10% long-chain fructo-oligosaccharides (inulin extracted from chicory roots, average degree of polymerization > 23) (scGOS/lcFOS) was developed which closely resembles the molecular size distribution of HMO[9,26]. Many studies have been done with this mixture and most of these studies focused on the beneficial effects of scGOS/lcFOS (9:1) on the development of the intestinal microbiota and the maturation of the immune system and measured stool characteristics as secondary outcomes[27]. However, like HMO, fermentation of non-digestible oligosaccharides can potentially benefit faecal characteristics[28]. A review of the colonic effects of all different types of non-digestible oligosaccharides is beyond the scope of this paper. The current review specifically addresses the effects of a mixture of scGOS/lcFOS on faecal characteristics.

In most of the studies with scGOS/lcFOS, tolerance to infant formulas and stool characteristics have been taken into account as secondary outcome outcomes. Only a small number of studies have specifically addressed the effects of non-digestible oligosaccharides on stool characteristics as a primary focus. Furthermore, the different stool characteristics have not been measured with the same methodology, which makes it difficult to compare the outcomes of these studies systematically. However, as these measures have been taken into account in several of these studies, these effects and the potential mode of actions in the individual studies described below. Table 1 summarizes the studies that included effects of a specific mixture of scGOS/lcFOS on stool characteristics.

STOOL FREQUENCY AND STOOL CONSISTENCY

In a study by Costalos *et al*[29] an infant milk formula with 0.4 g/100 mL scGOS/lcFOS (9:1) was compared to a control formula without scGOS/lcFOS in term infants for 10 wk. Stool characteristics were included as secondary outcomes and data were obtained from a 5-d diary at the end of the intervention period. Effects on stool

Table 1 Summarizes the studies that included effects of a specific mixture of short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides on stool characteristics

Author	Age group	Dose	*n*	Outcome	Result in scGOS/lcFOS group
Costalos 2008	Term	0.4 g/100 mL	140 (2 groups)	Stool frequency	Statistically significant increase after 10 wk of intervention
				Stool consistency	Statistically significant softer stools after 10 wk of intervention
Moro 2002	Term	0.4/0.8 g/100 mL	90 (3 groups)	Stool frequency	Statistically significant increase after 4 wk of intervention
				Stool consistency	Statistically significant softer stools after 4 wk of intervention
Veereman 2011	Term	0.8 g/100 mL	76 (5 groups)	Stool frequency	No statistically significant differences
				Stool consistency	Statistically significant softer stools after 2 and 4 wk of intervention
Bisceglia 2009	Term	0.8 g/100 mL	76 (2 groups)	Stool frequency	Statistically significant increase throughout 4 wk of intervention
				Stool consistency	Not measured
Boehm 2002	Preterm	1.0 g/100 mL	42 (3 groups)	Stool frequency	Statistically significant increase after 4 wk of intervention
				Stool consistency	Statistically significant softer stools after 4 wk of intervention
Mihatsch 2006	Preterm	1.0 g/100 mL	20 (2 groups)	Stool frequency	No statistically significant differences
				Stool consistency	Results not provided
				Viscosity	Statistically significant lower viscosity after 2 wk of intervention
Modi 2010	Preterm	0.8 g/100 mL	150 (2 groups)	Stool frequency	No statistically significant differences
				Stool consistency	No statistically significant differences

scGOS/lcFOS: Short chain galacto-oligosaccharides and long-chain fructo-oligosaccharides.

consistency were rated on a 5-point scale, ranging from 1 = watery and 5 = hard. In this study, a statistically significant higher stool frequency and a statistically significant lower stool consistency (softer stools) were observed with the formula with scGOS/lcFOS when compared to the control formula. After 10 wk of intervention, the median number of stools per day was 1.9 and 1.6 in the scGOS/lcFOS (9:1) group and the control group respectively ($P = 0.031$). Stool consistency scores were 3 and 3.1 ($P = 0.026$) in the two groups respectively).

Moro *et al*[30] performed a study in term infants that received an infant milk formula with 0.4 g/100 mL or 0.8 g/100 mL scGOS/lcFOS (9:1) or a control formula without scGOS/lcFOS (9:1) for 28 d. In this study, stool characteristics were also included as secondary outcomes at baseline and after 28 d of intervention. Again, stool consistency was rated on a 5-point scale ranging from 1-watery to 5-hard. A statistically significant lower stool consistency (softer stools) and a statistically significant higher stool frequency were observed in infants that received the formula with 0.8 g/100 mL scGOS/lcFOS when compared to infants that received the control formula. At the end of the intervention, the median number of stools per day was 2 for both groups ($P < 0.01$), and stool consistency scores were 2.3 and 4 in the scGOS/lcFOS (9:1) group and the control group respectively ($P < 0.0001$).

In a study of Veereman-Wauters *et al*[31] a statistically significant lower stool consistency was observed in term infants after 2 and 4 wk of intervention with a formula with 0.8 g/100 mL scGOS/lcFOS (9:1) when compared to a control group without scGOS/lcFOS. Stool characteristics were included as secondary outcomes and were recorded in 3-d diaries at baseline, and after 2 and 4 wk of intervention. Stool consistency was measured on a 4-point scale ranging from 1-watery to 4-hard. Mean stool consistency scores were approximately 1.9 in the scGOS/lcFOS (9:1) group and 2.4 in the control group. In this study, a human milk reference group was included. In that group, the mean stool consistency was 1.3. No statistically significant differences were observed in stool frequency.

Bisceglia *et al*[32] followed a group of 36 term infants from birth until 28 d of life. The infants received a formula with 0.8 g/100 mL scGOS/lcFOS (9:1) or a control formula. Stool frequency was included as a secondary outcome. Stool frequency was recorded throughout the study, and a significantly higher number of stools were recorded in the scGOS/lcFOS (9:1) group when compared to the control group (3.4 and 1.7 stools per day, respectively, $P < 0.001$). In this study, stool consistency has not been recorded.

The studies summarized above focused on effects of scGOS/lcFOS in term infants, but studies in preterm infants show similar effects. In preterm infants, gastrointestinal tolerance to formula feeding is an important aspect, and enteral feeding can be associated with a disturbed gastrointestinal passage. One of the studies with scGOS/lcFOS in preterm infants specifically focused on stool characteristics as a primary outcome. In this study, Mihatsch *et al*[33] observed statistically significant effects of an infant milk formula with 1.0 g/100 mL scGOS/lcFOS (9:1) on stool viscosity and gastrointestinal transit time, but did not demonstrate an effect on stool frequency after 14 d of intervention in preterm infants. Stool viscosity and gastrointestinal transit time were the primary outcomes in this study. Stool characteristics were recorded throughout the study. Stool consistency was shown as a percentage of each type of consistency (hard, formed, soft, mushy or watery) against all stools throughout the study. A higher proportion of soft stools were observed in the infants that received scGOS/lcFOS (9:1) when compared to infants receiving a control formula without scGOS/lcFOS, but no information on the statistical significance is provided in the paper. The median stool viscosity (measured as extrusion force) was significantly lower in the scGOS/lcFOS group when compared to the control group, with a level of 31.8 mol/L and 157.5 mol/

L in the two groups respectively ($P = 0.006$). In addition, a shorter transit time (12 h) was observed in preterm infants that had received a formula with scGOS/lcFOS, when compared to infants who had received a control formula (25.6 h)[33]. In this study, the difference in the change in transit time between the groups from baseline to day 14 was statistically significant (6 h decreased transit time in the scGOS/lcFOS group, and a 9.1 h increased transit time in the control group). The total number of stools did not show a statistically significant difference, but there was a trend toward a higher stool frequency in the scGOS/lcFOS (9:1) group when compared to the control group (3.6 and 2.6 respectively ($P = 0.059$).

Boehm *et al*[34] showed a statistically significant lower stool consistency (softer stools) and a statistically significant higher stool frequency in preterm infants receiving an infant milk formula with 1.0 g/100 mL scGOS/lcFOS (9:1) when compared to infants receiving an infant milk formula without scGOS/lcFOS. In this study, stool characteristics were included as secondary outcomes and data were collected via questionnaires. After 28 d of intervention, a mean number of stools of 2.2 and 1.3 in the scGOS/lcFOS (9:1) and control groups, respectively, was observed ($P = 0.0079$), and a mean stool consistency score of 2.7 and 3.5 in both groups respectively ($P = 0.0102$, mean score from a 5-point scale ranging from 1-watery to 5-hard).

Modi *et al*[35] did not find statistically significant differences in stool frequency and stool consistency between a scGOS/lcFOS (9:1) group (0.8 g/100 mL) and a control group of preterm infants. The intervention lasted from preterm birth until hospital discharge, for a maximum of 12 wk. Stool characteristics were included as secondary outcomes. In this study, a statistically significant effect may not have been observed as stool consistency scores were not based on diary data, but on a single observation of the hospital staff[35]. Furthermore, in this study, formula was supplied in addition to human milk, and the number of children exclusively receiving formula was very low (15%). As human milk may already have a significant effect on stool characteristics, the effect of addition of a limited amount of formula with or without scGOS/lcFOS may not have been visible.

POSSIBLE MECHANISMS OF ACTION

The potential beneficial effects of scGOS/lcFOS on stool characteristics can be mediated by the increase in microbial mass, selective fermentation and production of SCFA, stimulation of gastrointestinal motility, or the direct effects of the provided dietary fibers in the form of scGOS/lcFOS.

The specific mixture of scGOS/lcFOS (9:1) is a mixture of oligosaccharides that is not digested in the gastrointestinal tract and is available for fermentation in the colon[36,37]. Indeed, this mixture has been shown to increase the total concentrations and the individual concentrations and percentages of bifidobacteria and lactobacilli in the colon[29-31,34,36,38-42]. For instance, in the study by Moro *et al*[30] levels of bifidobacteria increased after 28 d of intervention to 9.3 CFU/g faeces in infants who received a formula with 0.4 g/100 mL scGOS/lcFOS, and to 9.7 CFU/g faeces in infants who received a formula with 0.8 g/100 mL scGOS/lcFOS. In the control group, a level of bifidobacteria of 7.2 CFU/g faeces was observed. In a study by Scholtens *et al*[43] intervention with infant milk formulas with 0.6 g/100 mL resulted in higher percentages of bifidobacteria after 26 wk of intervention (59.8% *vs* 47.2% in the scGOS/lcFOS group and the control group respectively). An increased microbial mass may partly explain the stool softening effect associated with infant milk formulas containing the specific scGOS/lcFOS (9:1) mixture compared to infant milk formulas lacking these oligosaccharides.

As mentioned before, selective fermentation of non-digestible components in the colon results in the production of SCFA. Infant milk formulas with scGOS/lcFOS (9:1) have indeed been shown to affect the production of SCFA, and to provide a faecal SCFA profile that is close to that of human milk fed infants, with higher percentages of acetate and lower percentages of propionate and butyrate[36,40]. In a study by Knol *et al*[40] the percentages of acetate, propionate and butyrate were 85.2%, 12% and 2.4% respectively in infants who received a formula with scGOS/lcFOS for 6 wk. In the control group, these percentages were 77.2%, 17.8% and 4% respectively after 6 wk of intervention. As SCFA can affect stool characteristics *via* stimulation of gastrointestinal motility by being used as energy source for colonic epithelial cells, or by inducing phasic and tonic contractions in circular muscle[21-25], scGOS/lcFOS (9:1) may positively stimulate the gastrointestinal motility.

NDO may also stimulate upper gastrointestinal motility. In a study bv Indrio *et al*[44] a beneficial effect of scGOS/lcFOS (9:1) on gastric emptying time was observed in preterm infants that received a formula with 0.8 g/L scGOS/lcFOS (9:1) or a control formula. In this study, it is suggested that the production of SCFA in the scGOS/lcFOS (9:1) group was responsible for an increased upper gastrointestinal motility, observed as a significant increased percentage propagation (assessed by electrogastrography) in the scGOS/lcFOS group when comped to the placebo group, and increased gastric emptying rate, observed as lower half emptying time in the scGOS/lcFOS group than in the placebo group[45]. As mentioned before, similar results have been observed in the study by Mihatsch *et al*[33] with a significantly shorter transit time (12 h) in preterm infants that had received a formula with scGOS/lcFOS, when compared to infants who had received a control formula (25.6 h) for 14 d. The gastrointestinal transit time measured in this study in the scGOS/lcFOS (9:1) group was mentioned to be within the normal range of what is observed human milk-fed infants (not further specified in the paper).

Both a direct effect as well as fermentation related effects can be affected by the type and structure of NDO[46]. The specific mixture of scGOS/lcFOS (9:1) consists of a combination of short-chain galacto-oligo-

saccharides and long-chain fructo-oligosaccharides in a ratio of 9:1. The composition and ratio of this specific mixture was specifically developed to closely resemble the molecular size composition of HMO (assessed by Mass Spectrometry)[26]. *In vitro* studies have indicated that short chain oligosaccharides are mainly fermented in the proximal part of the colon, while longer-chain NDO are mainly fermented in the distal colon[47]. Indeed, in a study by Moro *et al*[27] it was shown that part of the scGOS/lcFOS (9:1) is still detectable in faeces of infants, indicating that even in the distal part of the colon, not all scGOS/lcFOS (9:1) is fermented. This indicates that scGOS/lcFOS (9:1) can be effective throughout the whole gastrointestinal tract.

Although a direct correlation between stool consistency and/or stool frequency and bowel habit has never been shown, both stool frequency and stool consistency have often been used to assess bowel habit in a daily or clinical setting[48]. Recently, Russo *et al*[48] indicated that especially stool consistency is correlated with whole gut transit time, and that stool frequency is a poor marker for whole gut transit time. As described in the study of Mihatsch *et al*[33] with scGOS/lcFOS (9:1), gut transit time was assessed in preterm infants. In this study, gut transit time was significantly shorter in preterm infants receiving an infant milk formula with scGOS/lcFOS (9:1) when compared to an infant milk formula without scGOS/lcFOS (9:1). As an increased whole gut transit time can be a risk factor in the onset of constipation[49], scGOS/lcFOS (9:1) may have clinical relevance in the prevention of constipation by reducing whole gut transit time.

Effects of scGOS/lcFOS (9:1) on stool frequency were less often observed than effects on stool consistency. This can be due to the fact that the method of assessing stool frequency. The assessment of stool frequency was often done by the collection of faeces-containing diapers. However, it is difficult to assess whether a diaper contains one or more stooling episodes, and therefore, data collection may be less accurate. This may explain why effects on stool frequency are less commonly observed than effects on stool consistency. However, for these young infants there are no other methods available for a more accurate measurement of stool frequency.

CONCLUSION

In several of the studies with scGOS/lcFOS in a ratio of 9:1 in infant milk formulas, positive effects of this mixture on stool characteristics such as stool consistency and stool frequency were observed. Effects on stool consistency were more often found to be significant than the effects on stool frequency. As stool consistency has been shown to be correlated to whole gut transit time, stool softening effects of scGOS/lcFOS (9:1) may have a benefit in reducing the risk of constipation. This is crucial for the prevention of this very common functional gastrointestinal disorder in the general population, since one third of children followed up beyond the puberty continue to have severe complaints of constipation[50].

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REFERENCES

1 **van den Berg MM**, Benninga MA, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. *Am J Gastroenterol* 2006; **101**: 2401-2409 [PMID: 17032205 DOI: 10.1111/j.1572-0241.2006.00771.x]
2 **Hyman PE**, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiau J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006; **130**: 1519-1526 [PMID: 16678565 DOI: 10.1053/j.gastro.2005.11.065]
3 **Partin JC**, Hamill SK, Fischel JE, Partin JS. Painful defecation and fecal soiling in children. *Pediatrics* 1992; **89**: 1007-1009 [PMID: 1594338]
4 **Borowitz SM**, Cox DJ, Tam A, Ritterband LM, Sutphen JL, Penberthy JK. Precipitants of constipation during early childhood. *J Am Board Fam Pract* 2003; **16**: 213-218 [PMID: 12755248 DOI: 10.3122/jabfm.16.3.213]
5 **Davidson M**, Kugler MM, Bauer CH. Diagnosis and management in children with severe and protracted constipation and obstipation. *J Pediatr* 1963; **62**: 261-275 [PMID: 14025378 DOI: 10.1016/S0022-3476(63)80404-7]
6 **Iacono G**, Merolla R, D'Amico D, Bonci E, Cavataio F, Di Prima L, Scalici C, Indinnimeo L, Averna MR, Carroccio A. Gastrointestinal symptoms in infancy: a population-based prospective study. *Dig Liver Dis* 2005; **37**: 432-438 [PMID: 15893282 DOI: 10.1016/j.dld.2005.01.009]
7 **Quinlan PT**, Lockton S, Irwin J, Lucas AL. The relationship between stool hardness and stool composition in breast- and formula-fed infants. *J Pediatr Gastroenterol Nutr* 1995; **20**: 81-90 [DOI: 10.1097/00005176-199501000-00014]
8 **Weaver LT**, Ewing G, Taylor LC. The bowel habit of milk-fed infants. *J Pediatr Gastroenterol Nutr* 1988; **7**: 568-571 [PMID: 3397847 DOI: 10.1097/00005176-198807000-00015]
9 **Stahl B**, Thurl S, Zeng J, Karas M, Hillenkamp F, Steup M, Sawatzki G. Oligosaccharides from human milk as revealed by matrix-assisted laser desorption/ionization mass spectrometry. *Anal Biochem* 1994; **223**: 218-226 [PMID: 7887467 DOI: 10.1006/abio.1994.1577]
10 **Kunz C**, Rudloff S, Baier W, Klein N, Strobel S. Oligosaccharides in human milk: structural, functional, and metabolic aspects. *Annu Rev Nutr* 2000; **20**: 699-722 [PMID: 10940350 DOI: 10.1146/annurev.nutr.20.1.699]
11 **Gibson GR**, Prebiotics, Oligosaccharides. Dietary modulation of the human gut microflora using prebiotics. *Br J Nutr* 1998; **80**: S209-212
12 **Gibson GR**, Probert HM, Loo JV, Rastall RA, Roberfroid MB. Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. *Nutr Res Rev* 2004; **17**: 259-275 [PMID: 19079930 DOI: 10.1079/NRR200479]
13 **Macfarlane S**, Macfarlane GT, Cummings JH. Review article: prebiotics in the gastrointestinal tract. *Aliment Pharmacol Ther* 2006; **24**: 701-714 [PMID: 16918875 DOI: 10.1111/j.1365-2036.2006.03042.x]
14 **Roberfroid M**, Slavin J. Nondigestible oligosaccharides. *Critical Reviews in Food Science and Nutrition* 2000; **40**: 461-480 [DOI: 10.1080/10408690091189239]
15 **Roberfroid M**, Gibson GR, Hoyles L, McCartney AL, Rastall R, Rowland I, Wolvers D, Watzl B, Szajewska H, Stahl B, Guarner F, Respondek F, Whelan K, Coxam V, Davicco MJ, Léotoing L, Wittrant Y, Delzenne NM, Cani PD, Neyrinck

AM, Meheust A. Prebiotic effects: metabolic and health benefits. *Br J Nutr* 2010; **104** Suppl 2: S1-63 [PMID: 20920376 DOI: 10.1017/S0007114510003363]
16 **Mortensen PB**, Clausen MR. Short-chain fatty acids in the human colon: relation to gastrointestinal health and disease. *Scand J Gastroenterol Suppl* 1996; **216**: 132-148 [PMID: 8726286 DOI: 10.3109/00365529609094568]
17 **Lidestri M**, Agosti M, Marini A, Boehm G. Oligosaccharides might stimulate calcium absorption in formula-fed preterm infants. *Acta Paediatr Suppl* 2003; **91**: 91-92 [PMID: 14599050]
18 **Roberfroid MB**. Introducing inulin-type fructans. *Br J Nutr* 2005; **93** Suppl 1: S13-S25 [PMID: 15877886 DOI: 10.1079/BJN20041350]
19 **Cummings JH**. Constipation, dietary fibre and the control of large bowel function. *Postgrad Med J* 1984; **60**: 811-819 [PMID: 6095241 DOI: 10.1136/pgmj.60.709.811]
20 **Roberfroid M**. Dietary fiber, inulin, and oligofructose: a review comparing their physiological effects. *Crit Rev Food Sci Nutr* 1993; **33**: 103-148 [PMID: 8257475 DOI: 10.1080/10408399309527616]
21 **Cherbut C**. Motor effects of short-chain fatty acids and lactate in the gastrointestinal tract. *Proc Nutr Soc* 2003; **62**: 95-99 [PMID: 12740048 DOI: 10.1079/PNS2002213]
22 **Van Loo J**, Cummings J, Delzenne N, Englyst H, Franck A, Hopkins M, Kok N, Macfarlane G, Newton D, Quigley M, Roberfroid M, van Vliet T, van den Heuvel E. Functional food properties of non-digestible oligosaccharides: a consensus report from the ENDO project (DGXII AIRII-CT94-1095). *Br J Nutr* 1999; **81**: 121-132 [PMID: 10450330]
23 **Cebra JJ**. Influences of microbiota on intestinal immune system development. *Am J Clin Nutr* 1999; **69**: 1046S-1051S [PMID: 10232647]
24 **Tazoe H**, Otomo Y, Kaji I, Tanaka R, Karaki SI, Kuwahara A. Roles of short-chain fatty acids receptors, GPR41 and GPR43 on colonic functions. *J Physiol Pharmacol* 2008; **59** (Suppl 2): 251-262[PMID: 18812643]
25 **Yajima T**. Contractile effect of short-chain fatty acids on the isolated colon of the rat. *J Physiol* 1985; **368**: 667-678 [PMID: 2867220]
26 **Boehm G**, Fanaro S, Jelinek J, Stahl B, Marini A. Prebiotic concept for infant nutrition. *Acta Paediatr Suppl* 2003; **91**: 64-67 [PMID: 14599044]
27 **Moro GE**, Boehm G. Clinical Outcomes of Prebiotic Intervention Trials during Infancy: A Review. *Func Food Rev* 2012; **4**: 000-000
28 **Macfarlane GT**, Steed H, Macfarlane S. Bacterial metabolism and health-related effects of galacto-oligosaccharides and other prebiotics. *J Appl Microbiol* 2008; **104**: 305-344 [PMID: 18215222]
29 **Costalos C**, Kapiki A, Apostolou M, Papathoma E. The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. *Early Hum Dev* 2008; **84**: 45-49 [PMID: 17433577 DOI: 10.1016/j.earlhumdev.2007.03.001]
30 **Moro G**, Minoli I, Mosca M, Fanaro S, Jelinek J, Stahl B, Boehm G. Dosage-related bifidogenic effects of galacto- and fructooligosaccharides in formula-fed term infants. *J Pediatr Gastroenterol Nutr* 2002; **34**: 291-295 [PMID: 11964956 DOI: 10.1097/00005176-200203000-00014]
31 **Veereman-Wauters G**, Staelens S, Van de Broek H, Plaskie K, Wesling F, Roger LC, McCartney AL, Assam P. Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *J Pediatr Gastroenterol Nutr* 2011; **52**: 763-771 [PMID: 21593649 DOI: 10.1097/MPG.0b013e3182139f39]
32 **Bisceglia M**, Indrio F, Riezzo G, Poerio V, Corapi U, Raimondi F. The effect of prebiotics in the management of neonatal hyperbilirubinaemia. *Acta Paediatr* 2009; **98**: 1579-1581 [PMID: 19555446 DOI: 10.1111/j.1651-2227.2009.01387.x]
33 **Mihatsch WA**, Hoegel J, Pohlandt F. Prebiotic oligosaccharides reduce stool viscosity and accelerate gastrointestinal transport in preterm infants. *Acta Paediatr* 2006; **95**: 843-848 [PMID: 16801182 DOI: 10.1080/08035250500486652]
34 **Boehm G**, Lidestri M, Casetta P, Jelinek J, Negretti F, Stahl B, Marini A. Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Arch Dis Child Fetal Neonetal Ed* 2002; **86**: F178-181[PMID: 11978748]
35 **Modi N**, Uthaya S, Fell J, Kulinskaya E. A randomized, double-blind, controlled trial of the effect of prebiotic oligosaccharides on enteral tolerance in preterm infants (ISRCTN77444690). *Pediatr Res* 2010; **68**: 440-445 [PMID: 20639792 DOI: 10.1203/PDR.0b013e3181f1cd59]
36 **Boehm G**, Moro G. Structural and functional aspects of prebiotics used in infant nutrition. *J Nutr* 2008; **138**: 1818S-1828S [PMID: 18716193]
37 **Moro GE**, Stahl B, Fanaro S, Jelinek J, Boehm G, Coppa GV. Dietary prebiotic oligosaccharides are detectable in the faeces of formula-fed infants. *Acta Paediatr Suppl* 2005; **94**: 27-30 [PMID: 16214762 DOI: 10.1080/08035320510043510]
38 **Haarman M**, Knol J. Quantitative real-time PCR assays to identify and quantify fecal Bifidobacterium species in infants receiving a prebiotic infant formula. *Appl Environ Microbiol* 2005; **71**: 2318-2324 [PMID: 15870317 DOI: 10.1128/AEM.71.5.2318-2324.2005]
39 **Haarman M**, Knol J. Quantitative real-time PCR analysis of fecal Lactobacillus species in infants receiving a prebiotic infant formula. *Appl Environ Microbiol* 2006; **72**: 2359-2365 [PMID: 16597930 DOI: 10.1128/AEM.72.4.2359-2365.2006]
40 **Knol J**, Scholtens P, Kafka C, Steenbakkers J, Gro S, Helm K, Klarczyk M, Schöpfer H, Böckler HM, Wells J. Colon microflora in infants fed formula with galacto- and fructo-oligosaccharides: more like breast-fed infants. *J Pediatr Gastroenterol Nutr* 2005; **40**: 36-42 [PMID: 15625424 DOI: 10.1097/00005176-200501000-00007]
41 **Moro G**, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child* 2006; **91**: 814-819 [PMID: 16873437 DOI: 10.1136/adc.2006.098251]
42 **Scholtens PA**, Alles MS, Bindels JG, van der Linde EG, Tolboom JJ, Knol J. Bifidogenic effects of solid weaning foods with added prebiotic oligosaccharides: a randomised controlled clinical trial. *J Pediatr Gastroenterol Nutr* 2006; **42**: 553-559 [PMID: 16707980 DOI: 10.1097/01.mpg.0000221887.28877.c7]
43 **Scholtens PA**, Alliet P, Raes M, Alles MS, Kroes H, Boehm G, Knippels LM, Knol J, Vandenplas Y. Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. *J Nutr* 2008; **138**: 1141-1147 [PMID: 18492847]
44 **Indrio F**, Riezzo G, Raimondi F, Francavilla R, Montagna O, Valenzano ML, Cavallo L, Boehm G. Prebiotics improve gastric motility and gastric electrical activity in preterm newborns. *J Pediatr Gastroenterol Nutr* 2009; **49**: 258-261 [PMID: 19561548 DOI: 10.1097/MPG.0b013e3181926aec]
45 **Labayen I**, Forga L, González A, Lenoir-Wijnkoop I, Nutr R, Martínez JA. Relationship between lactose digestion, gastrointestinal transit time and symptoms in lactose malabsorbers after dairy consumption. *Aliment Pharmacol Ther* 2001; **15**: 543-549 [PMID: 11284784 DOI: 10.1046/j.1365-2036.2001.00952.x]
46 **Kelly G**. Inulin-type prebiotics--a review: part 1. *Altern Med Rev* 2008; **13**: 315-329 [PMID: 19152479]
47 **Stewart ML**, Timm DA, Slavin JL.Fructooligosaccharides exhibit more rapid fermentation than long-chain inulin in an in vitro fermentation system. *Nutr Res* 2008; **28**: 329-334 [PMID: 19083428 DOI: 10.1016/j.nutres.2008.02.014]
48 **Russo M**, Martinelli M, Sciorio E, Botta C, Miele E, Vallone G, Staiano A. Stool consistency, but not frequency, correlates with total gastrointestinal transit time in children. *J*

Pediatr 2013; **162**: 1188-1192 [PMID: 23312678 DOI: 10.1016/j.jpeds.2012.11.082]

49 **Gutiérrez C**, Marco A, Nogales A, Tebar R. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. *J Pediatr Gastroenterol Nutr* 2002; **35**: 31-38 [PMID: 12142807]

50 **van Ginkel R**, Reitsma JB, Büller HA, van Wijk MP, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond puberty. *Gastroenterology* 2003; **125**: 357-363 [PMID: 12891536]

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