

Supplementary Material 5

Evidence of effectiveness - Level 0 synthesis – Additional tables

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Table 1: Characteristics of Excluded Studies

Study	Reason for exclusion
Systematic reviews judged to be at high/unclear risk of bias or to overlap with a more up-to-date or comprehensive systematic review (n=15)	
Axelrod 2018 ¹	Intervention addressed: Fibre ROB assessment: High ROB Reason for exclusion: Not low ROB
Boilesen 2017 ²	Intervention addressed: Fluid intake ROB assessment: High ROB Reason for exclusion: Not low ROB
Dziechciarz 2015 ³	Intervention addressed: Laxative ROB assessment: Low ROB Reason for exclusion: Superseded by Morris (see Level 1 synthesis)
Freeman 2014 ⁴	Intervention addressed: Psychosocial ROB assessment: Low ROB Reason for exclusion: Moved to Psychosocial
Gartlehner 2007 ⁵	Intervention addressed: OTC laxatives ROB assessment: Low ROB Reason for exclusion: Superseded by Morris (see Level 1 synthesis)
Gomes 2019 ⁶	Intervention addressed: Probiotics ROB assessment: Unclear ROB Reason for exclusion: Not low ROB
Jin 2018 ⁷	Intervention addressed: Probiotics ROB assessment: Low ROB Reason for exclusion: Superseded by Harris 2019
Huang 2017 ⁸	Intervention addressed: Probiotics ROB assessment: Low ROB Reason for exclusion: Superseded by Harris 2019
Koppen 2016 ⁹	Intervention addressed: Probiotics, Fibre ROB assessment: Unclear ROB

	Reason for exclusion: Not low ROB
Kortering 2014 ¹⁰	Intervention addressed: Probiotics ROB assessment: Low ROB Reason for exclusion: Superseded by Harris 2019
Tabbers 2011 ¹¹	Intervention addressed: Non-pharmacological ROB assessment: High ROB Reason for exclusion: Not low ROB
Tabbers 2015 ¹²	Intervention addressed: Probiotics, Fibre ROB assessment: High ROB Reason for exclusion: Not low ROB
Wegh 2018 ¹³	Intervention addressed: Probiotics ROB assessment: High ROB Reason for exclusion: Not low ROB
Wojtyniak 2017 ¹⁴	Intervention addressed: Probiotics ROB assessment: Low ROB Reason for exclusion: Superseded by Harris 2019
Yang 2012 ¹⁵	Intervention addressed: Fibre ROB assessment: Unclear ROB Reason for exclusion: Not low ROB
Studies judged not to meet inclusion criteria (n=55)	
Bellomo-Brandao 2018 ¹⁶	The focus is on antegrade continence enema (ACE), therefore this study fits under “Level 3”. Included in Level 3 synthesis.
Brazzelli 2011 ¹⁷	Aim: The aim of this review is to summarise systematically evidence from all relevant randomised controlled trials on the effects of behavioural (including biofeedback training) and cognitive therapies with or without other treatments for the management of children defaecation disorders in order to provide the best evidence currently available on which to base recommendations for clinical practice. Interventions included are not relevant to our question of “What is the effectiveness of ‘everyday life’ interventions delivered by carers, without the involvement of healthcare professionals?”. This review is relevant to other questions in this systematic review.
Campeotto 2020 ¹⁸	Aim: To estimate the frequency of functional gastrointestinal disorders (FGIDs) in infants aged up to 12 months according to the new ROME IV criteria defining these disorders, and to describe the management of FGIDs in France.

	This observational study does not explore effectiveness of interventions.
Carroccio 2005 ¹⁹	Population is children with cows milk allergy and constipation, therefore exclude.
Chase 2011 ²⁰	Aim: The primary aim of this systematic review was to establish the efficacy of non-pharmacological, non-surgical and non-behavioural treatments of functional chronic constipation in children. A secondary aim was to identify any of nonpharmacological, non-surgical and non-behavioural treatments of functional chronic constipation, used either alone or in combination with pharmacological, surgical and behavioural interventions. The studies included in this review focussed on interventions that were alternative therapies, or interventions delivered by health professionals; therefore not relevant to this question/Level 0.
Ciullo 2015 ²¹	Study is a survey of delivered interventions; no focus on effectiveness
Coehlo 2011 ²²	Single case study
Coffey 2017 ²³	Study is focussed on management and impact of constipation; no focus on effectiveness
Crowley 2013 ²⁴	Paper reports two cross-over studies investigating cow's milk intolerance and the effect of cow's milk free diet on constipation. Consensus discussion led to decision to exclude, as participants with cow's milk allergy are not eligible for our review.
Our Lady's Hospital for Sick Children 2016 ²⁵	Included in 'Care provision' synthesis.
El-Shabrawi 2018 ²⁶	Intervention is based on clinical guidelines, with a focus on manometry. Included in Level 1 synthesis.
Esmaelidooki 2016 ²⁷	RCT focussed on laxatives; for consideration in review update within Level 1 synthesis. Has a comparison with cassia fistula, and is included within the included systematic review relating to cassia fistula.
Fontanele Soares 2009 ²⁸	Children were seen at a constipation clinic, therefore included in Level 1 synthesis.
Gabr 2020 ²⁹	Focus is on a bowel management program, delivered via a clinic, therefore relevant to "service delivery". Included in 'Care provision' synthesis.
Garcia 2016 ³⁰	Intervention is delivered to hospital in-patients. Included in Level 2 synthesis.
Gonring 2019 ³¹	Intervention is an "interdisciplinary" approach, based on group treatment, led by an Advanced Nurse Practitioner. Included in Level 2 synthesis.
Horvath 2013 ³²	Aim: To systematically evaluate the effect of dietary fibers for treating abdominal pain-related FGIDs in children. Provides follow-up data for two RCTs (would be relevant data if those RCTs are included)
Jang 2019 ^{33, 34}	Study is a survey of delivered interventions; no focus on effectiveness
Jordan-Ely 2013 ³⁵	Intervention is an educational programme administered in a nurse led clinic. Included in Level 1 synthesis.
Jordan-Ely 2013 ³⁶	Intervention is delivered by a nurse. Considered (and then excluded from) Level 2 synthesis (as there is a systematic

	review of this intervention).
Khatibshahidi 2013 ³⁷	Insufficient details – published as an abstract only, with insufficient information to determine the study design. Describes two treatment groups, but no details relating to allocation.
Koppen 20017 ³⁸	Study is a survey of delivered interventions; no focus on effectiveness
Librizzi 2017 ³⁹	Focus is on treatments given to hospitalised patients. Considered (and then excluded from) Level 2 synthesis.
Loening-Baucke 1993 ⁴⁰	Intervention is health professional delivered. Included in Level 2 synthesis.
Loening-Baucke 1990 ⁴¹	Intervention is biofeedback. Included in Level 2 synthesis.
Lomas Mevers 2020 ⁴²	Intervention is delivered in an outpatient setting. Included in Level 1 synthesis.
Mahon 2017 ⁴³	Aim: To estimate the cost of FGIDs and related signs and symptoms in infants to the third party payer and to parents. Focus is on cost and not on intervention effectiveness.
Speridião (2003) ⁴⁴	Intervention includes rectal disimpaction. Included in Level 1 synthesis.
Nath 2017 ⁴⁵	Focus is on alternative therapies – move to complementary
Norbedo 2017 ⁴⁶	Focus is on management within the emergency department. Included in ‘Care provision’ synthesis.
Ostaszkiwicz 2005B ⁴⁷	Aim: To evaluate the relationship between constipation or faecal impaction and urinary incontinence (UI) and other lower urinary tract symptoms (LUTS). Focus is on relationship between symptoms and not on intervention effectiveness.
Peck 2017 ⁴⁸	Included in ‘Care provision’ synthesis.
Peleg 2017 (NCT03333070) ⁴⁹	Study of The Use of Lactobacillus Reuteri in Functional Constipation in Children. Trial reported as terminated as the PI has ended her work and no replacement was found to continue the trial.
Penuelas Calvo 2016 ⁵⁰	Included in Level 1 synthesis. Included in Level 1 synthesis.
Puoti 2019 ⁵¹	Intervention is “multidisciplinary approach”. This fits under our “service delivery” question and this study will be included in the evidence for this. Included in ‘Care provision’ synthesis.
Raghu 2019 ⁵²	Focus is on a clinical pathway. Included in ‘Care provision’ synthesis.
Ravanbakhsh 2019 ⁵³ IRCT20190614043891N	Intervention is visceral manipulation – moved to complementary synthesis.
Ritterband 2005 ⁵⁴	Reports a non-comparative study exploring website training, with no relevant outcomes measured.
Rogers 2014 ⁵⁵	Reports development of a toolkit with no outcomes measured.
Ruan 2018 ⁵⁶	Available as an abstract only, does not clearly meet inclusion criteria as the intervention and outcomes were focussed on parents of children with constipation.
Santucci 2020 ⁵⁷	Intervention is delivered by a Paediatric Gastroenterologist. Considered (and then excluded from) Level 2 synthesis.

Scarpato 2017 ⁵⁸	Focus is on alternative therapies – move to complementary
Silverman 2013 ⁵⁹	Observational study exploring management practices of children with functional constipation and fecal incontinence; aim of study was to compare management strategies for the two condition. Limited information available, as reported as abstract only. Intervention includes pharmacological interventions. Considered (and then excluded from) Level 1 synthesis
Steiner 2011 ⁶⁰	Focus is on adherence to treatment, rather than effectiveness. Consider within implementation review.
Stienen 2011 ⁶¹	Focus is on the development of quality indicators, rather than on evaluation of effectiveness on clinical outcomes.
Tabbers 2010 ⁶²	Aim: What are the effects of treatments for children with chronic constipation? What are the effects of treatments for clearing the bowel in children with faecal impaction? Focus is on primary care or specialist services; therefore not relevant to this question / Level 0
Tabbers 2014 ⁶³	Aim: The present guidelines provides recommendations for the diagnostic evaluation of children with functional constipation. This paper is a report of a guideline, rather than a systematic review
Thompson (2021) ⁶⁴	Systematic review addressing questions: 1. What are parents’ experiences of caring for a child with functional constipation (FC)? 2. What information do parents need to understand pediatric FC, make child-health decisions related to pediatric FC, and feel supported when caring for a child with FC? This systematic is focussed on experiences as is not a review of effect of interventions, therefore exclude.
Trinkley 2015 ⁶⁵	Focus is on patterns of prescription, but in relation to national guidance – so potentially relevant to “service delivery”. Considered for (and then excluded from) ‘Care provision’ synthesis.
van Tilburg 2012 ⁶⁶	Study explores parents perceptions and knowledge of constipation; no focus on effectiveness
Waingankar 2018 ⁶⁷	Intervention is delivered to patients who “have severe chronic constipation that has not resolved with years of treatment by general practitioners, pediatricians, or gastroenterologists”; this should be considered under Level 3.
Widodo 2018 ⁶⁸	Study is a survey of delivered interventions; no focus on effectiveness
Yang 2014 ⁶⁹	Study is a survey of delivered interventions; no focus on effectiveness
Yang 2015 ⁷⁰	Focus is on the adherence to clinical guidelines, rather than on evaluation of effectiveness of clinical outcomes
Zaja 2021 ^{71, 72}	RCT focussed on probiotics in children with anorexia nervosa. Inclusion criteria were that children had anorexia nervosa and constipation, however the included population "were severely underweight and in the restorative phase of nutrition". The decision was therefore made that this study did not meet the inclusion criteria for our review.

Table 2: Characteristics of ongoing studies

Study	Aim	Study design	Anticipated completion date
Systematic reviews (n=5)			
Fernandes 2018 ⁷³	Is Lactobacillus reuteri DSM 17938 effective and safe in childhood pathologies?	Systematic review	December 2018
Chau 2016 ⁷⁴	"Clinical efficacy and safety of probiotics in paediatric gastroenterology: an overview of systematic reviews"	Overview of reviews	2016 - ? never completed
Nanji 2012 ⁷⁵	To evaluate the efficacy and safety of fiber and bulking agents for the treatment of chronic constipation	Systematic review (Cochrane review protocol)	Not completed
Yang 2019 ⁷⁶	To investigate the effectiveness and safety of lacobacilli	Systematic review	Protocol
Capra 2003 ⁷⁷	to identify and present the best available evidence on dietetic treatment and management of constipation in children and adults	Systematic review	Unable to find published study
RCTs (n=23)			
Bagheri 2015 ⁷⁸ IRCT2015061722794 N1	To compare efficacy of brown sugar syrup and poly ethylene glycol (PEG) for treatment of constipation in children.	RCT	Not stated (First enrolment: 23-09-2015). Last updated February 2018.
Banavalikar 2017 ⁷⁹ CTRI/2017/11/010706	Straw Containing Sennoside with Probiotic of Inzpera Healthsciences Ltd. for Children from 5 to 12 years old having Functional constipation problem.	RCT	Reported as completed (15 participants) but unable to find a publication. Last checked: 28 May 2022.
Behnoud 2018 ⁸⁰ IRCT20171213037866 N1	Effects of Zizyphus Jujuba Fruit's product in the Childhood Functional Constipation	RCT	Registered 2018. States currently recruiting.
Belzer 2020 ⁸¹ NCT04282551	To study the effects of oligosaccharides vs a placebo on the change in stool consistency and stool frequency in children with functional constipation.	RCT	Ongoing. Estimated study completion November 2022.
Bishop 2014 ⁸² NCT02193997	To examine the effects of dietary fiber in treating functional childhood constipation	RCT	Reported as completed. Date of last entry is: 28/9/2017. No

			publications found.
Dziechciarz 2018 ⁸³ NCT03639142	Dried Plums (Prunes) vs. Polyethylene Glycol 4000 for Treatment of Functional Constipation in Children	RCT	Recruitment status is unknown. Last updated: 23/8/2018 Estimated study completion date: 1/11/2020. No publication found.
Eren 2013 ⁸⁴ NCT01913665	The Effect of Bifidobacterium Lactis and Inulin on Functional Constipation	RCT	Recruitment status reported as unknown. Last updated 7/8/2013. No publications found.
Guglielmo 2019 ⁸⁵ NCT03821532	This study is attempting to improve adherence, and outcomes, by implementing a trial of a constipation action plan plus standard of care, compared to standard of care alone, in an outpatient pediatric population. (Intervention is educational).	RCT	Reported as completed 31/1/2019. No publication found.
Jung 2017 ⁸⁶ NCT03030664	Effect of L. Reuteri on Bowel Movements in Children (BIOWELL Study)	RCT	Reported as completed. Date of last update: 6/8/2021. No publications found.
IRCT138812222434N (2015) ¹⁰⁰	The comparison between effect polyethylene glycol (PEG) Along with Bacillus coagulans (probiotic) with effect polyethylene glycol (PEG) in treatment of functional constipation in Childrens referred to pediatric gastroenterology clinic of Shiraz University of Medical Sciences	RCT	Retrospective registration. Unclear whether this study is completed, but no other publication was located.
Keihanian 2018 IRCT20131006014915 N3 ⁸⁷	Evaluation of Zyzyphus jujuba syrup in treatment of functional constipation in children	RCT	Recruitment is reported as complete but there is no publication found.
Kierkus 2011 ⁸⁸ NCT01388712	Lactobacillus Reuteri in Children with Constipation	RCT	Reported as recruiting 3/4/12. No other information available
Motavasselian 2019 ⁸⁹ IRCT20190122042459 N3	The effect of whey in the treatment of functional constipation in children	RCT	Still recruiting
Ordesa 2019 ⁹⁰ NCT04028258	Effect of a Mixture of Fibers and Carbohydrates on Intestinal Transit in Children Diagnosed With Functional	RCT	Recruitment status: unknown Last updated: 9/3/2020

	Constipation		Was expected to complete 12/2020. No publication found.
Parvani 2011 ⁹¹ IRCT201012275479N 1	Determination of the effects of toilet training in the treatment of functional constipation in children	RCT	Recruitment due to complete in 2011. No further information available.
Rafeey 2013 ⁹² IRCT201409015330N 7	Effect of probiotics in children constipation	RCT	Due to complete 2014. No further information available.
Sette 2014 ⁹³ NCT01901445	To determine if the quality of life in children and adolescents diagnosed with chronic functional constipation improves after educational activity in focus group composed by these patients' mothers.	RCT	Recruitment status reported as unknown. Last updated September 2013. Unable to find publication.
Sharif 2017 ⁹⁴ IRCT2013021112437 N1	Effects of Psyllium seed husk powder vs. Polyethylene glycol on constipation in children	RCT	States completion expected 2018. No publication found.
Souza 2015 ⁹⁵ RBR-2x8wqc	Randomized clinical trial double-blind efficacy of Prebiotics in Chronic Constipation Functional in infants	RCT	Registered 2015. Recruitment started 2011. Last checked 7/2/2022. Reported as still recruiting
Takazawa 2018 ⁹⁶ JPRN- UMIN000034508 (2018)	Examination of the diet cure for the pediatric constipation - assessment of the dietary fiber intake and the cow's milk allergy	RCT	Completed (11 participants recruited). Results posted online May 2022 (in Japanese: https://www.pref.gunma.jp/contents/100201634.pdf)
Tyrsin 2020 NCT04262648 ⁹⁷	Randomized Placebo-controlled Study of L. Reuteri NCIMB 30351 in GI Functional Disorders and Food Allergy in Newborns	RCT	Recruitment status: unknown Last updated: 12/2/2020 Was expected to complete 12/2020. No publication found.
Vásquez-Garibay 2017 NCT03117322 ⁹⁸	Synbiotic, Prebiotics and Probiotics in Children With Cerebral Palsy and Constipation	RCT	Reported as completed. Last updated: 26/12/2018. No publication found.
Weiss 2012	Treatment of Chronic Constipation in Children With	RCT	Recruitment status reported as

NCT01629147 ⁹⁹	Lactobacillus Reuteri		unknown. Last updated 22/5/2014. No publication found.
Xinhua hospital 2019 NCT03941925 ¹⁰⁰	Prebiotic Fructans Effect on 1-3 Years Constipated Children's Bowel Habits	RCT	Currently recruiting. Last updated: 12/7/21 Expected to complete in December 2022

Table 3: Studies awaiting assessment for inclusion in Level 0 synthesis

Study	Reason still awaiting assessment
Borowitz 2001 ¹⁰¹	Unable to access
Ghosh 2019 ¹⁰² CTRI/2019/04/018561	Ongoing study. Insufficient evidence to judge if this meets inclusion criteria.
Maffia 1955 ¹⁰³	Unable to access
Tolia 1993 ¹⁰⁴	Unable to access

Table 4: Risk of bias judgements for included systematic reviews, using ROBIS tool

	Domain 1: concerns regarding specification of study eligibility criteria	Domain 2: Concerns regarding methods used to identify and/or select studies	Domain 3: Concerns regarding methods used to collect data and appraise studies	Domain 4: Concerns regarding the synthesis and findings	Overall risk of bias in the review
Harris 2019 ¹⁰⁵	LOW	LOW	LOW	LOW	LOW
Piccoli de Mello 2018 ¹⁰⁶	LOW	LOW	UNCLEAR	LOW	LOW

Table 5: Risk of bias judgements for included controlled trials, using Cochrane ROB1 tool

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective reporting (reporting bias)
Aulia 2016 ¹⁰⁷	LOW risk	LOW risk	LOW risk	HIGH risk	UNCLEAR risk
Basturk 2017	UNCLEAR risk	LOW risk	LOW risk	LOW risk	UNCLEAR risk
Beleli 2015 ¹⁰⁸	HIGH risk	HIGH risk	LOW risk	LOW risk	LOW risk
Bongers 2007 ¹⁰⁹	UNCLEAR risk	LOW risk	LOW risk	HIGH risk	LOW risk
Mohammadi Bourkheili 2021 ¹¹⁰	UNCLEAR risk	HIGH risk	HIGH risk	HIGH risk	LOW risk
Cassettari 2019 ¹¹¹	HIGH risk	HIGH risk	HIGH risk	HIGH risk	UNCLEAR risk
Chao 2007 ¹¹²	LOW risk	UNCLEAR risk	HIGH risk	HIGH risk	LOW risk
Chao 2017 ¹¹³	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk
Closa-Monasterolo 2017 ¹¹⁴	LOW risk	LOW risk	LOW risk	HIGH risk	LOW risk
Deghani 2012 ¹¹⁵	LOW risk	UNCLEAR risk	HIGH risk	HIGH risk	LOW risk
Deghani 2019 ¹¹⁶	LOW risk	UNCLEAR risk	UNCLEAR risk	HIGH risk	LOW risk
Hassanein 2021 ¹¹⁷	LOW risk	LOW risk	LOW risk	LOW risk	LOW risk
Kubota 2020 ¹¹⁸	LOW risk	LOW risk	LOW risk	HIGH risk	UNCLEAR risk
Iacono 1998 ¹¹⁹	LOW risk	LOW risk	UNCLEAR risk	HIGH risk	LOW risk
Mahdavi 2017	LOW risk	UNCLEAR risk	HIGH risk	HIGH risk	HIGH risk
Mazzoni 2017 ¹²⁰	HIGH risk	HIGH risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk
Modaresi Saryazdi 2013 ¹²¹	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk
Ritterband 2003 ¹²²	UNCLEAR risk	HIGH risk	HIGH risk	HIGH risk	UNCLEAR risk
Ritterband 2013 ¹²³	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	HIGH risk	LOW risk
Sanctuary 2019 ¹²⁴	LOW risk	LOW risk	LOW risk	HIGH risk	LOW risk
Stepurina 2018 ¹²⁵	LOW risk	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	HIGH risk
Tajik 2018 ¹²⁶	LOW risk	UNCLEAR risk	HIGH risk	HIGH risk	UNCLEAR risk

Tanjung 2016 ¹²⁷	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	HIGH risk	LOW risk
Tayag-Lacsina 2019 ¹²⁸	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	HIGH risk	HIGH risk
Xinias 2018 ¹²⁹	HIGH risk	HIGH risk	HIGH risk	HIGH risk	HIGH risk
Young 1998 ¹³⁰	UNCLEAR risk	UNCLEAR risk	UNCLEAR risk	HIGH risk	UNCLEAR risk

Table 6: Risk of bias judgements for cohort studies, using CASP tool for cohort Studies

Study	Did the study address a clearly focused issue?	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors?	Have they taken account of the confounding factors in the design and/or analysis?	Was the follow up of subjects complete enough?	Was the follow up of subjects long enough?	Do you believe the results?	Can the results be applied to the population of interest?	OVERALL ASSESSMENT
Iacono 1995 131	yes	Can't tell	yes	Can't tell	No	Can't tell	Can't tell	yes	yes	yes	Minor concerns
Infante 2011 132	yes	Can't tell	Can't tell	yes	no	Can't tell	Can't tell	Can't tell	Can't tell	Can't tell	Moderate concerns
Infante Pina 2008 133	yes	yes	Can't tell	no	no	Can't tell	no	Can't tell	no	no	Serious concerns
Savino 2003 134	yes	yes	yes	no	no	Can't tell	no	no	no	no	Serious concerns

Table 7: Outcomes reported in Included Studies

Study	Outcomes Addressed								
	Painful defecation	QOL	Frequency	Consistency	Side Effects	Faecal Incontinence	Abdominal pain	School Attendance	Other
Beleli 2015 ¹⁰⁸	x		x	x					
Bongers 2007 ¹⁰⁹	x		x	x	x				abdominal and/or rectal mass
Mohammadi Bourkheili 2021 ¹¹⁰	x		x	x		x			Retentive posturing, constipation (based on Rome III) criteria
Chao 2007 ¹¹²			x	x					severity score based on stool consistence, frequency and volume, and difficulties in defecation, weight gain, abdominal distention, irritability.
Deghani 2012 ¹¹⁵	x		x	x		x			Retentive posturing or excessive stool retention
Deghani 2019 ¹¹⁶	x		x		x	x			Treatment success (based on Rome III criteria); rate of large fecal mass in the rectum; Effects on the body weight; Effects on serologic parameters; Patients' compliance
Hassanein 2021 ¹¹⁷			x	x					Time spent by mother in bowel evacuation attempts
Iacono 1998 ¹¹⁹	x		x	x					Rectal biopsies, histologic analysis

Study	Outcomes Addressed								
	Painful defecation	QOL	Frequency	Consistency	Side Effects	Faecal Incontinence	Abdominal pain	School Attendance	Other
Iacono 1995 ¹³¹	x		x	x					
Infante 2011 ¹³²	x			x					Stools at baseline and after 2 weeks of the adapted formula were assessed for faecal fat, water, carbohydrates, and protein
Mazzoni 2017 ¹²⁰				x					
Modaresi Saryazdi 2013 ¹²¹	x		x	x	x				“symptom free”
Infante Pina 2008 ¹³³	x		x	x	x				Prevalence of colic, constipation, regurgitation, diarrhoea. Satisfaction of the parents/tutors and paediatrician.
Ritterband 2003 ¹²²			x						Encopresis knowledge questionnaire, Virginia Encopresis/Constipation Apperception Test
Ritterband 2013 ¹²³	x		x	x		x		x	Encopresis knowledge scale-revised, Virginia Encopresis/Constipation Apperception Test, experiences of intervention, website usage, cost data
Savino 2003 ¹³⁴			x	x					Colic, regurgitation.
Stepurina 2018 ¹²⁵			x	x					Defecation difficulties or pain.
Tajik 2018 ¹²⁶	x		x	x	x	x	x		Anorexia
Tanjung 2016 ¹²⁷			x	x	x		x		
Tayag-Lacsina 2019 ¹²⁸			x	x					Dietary consumption, laxative intake.
Xinias 2018 ¹²⁹		x	x	x					
Young 1998 ¹³⁰			x	x					

Table 8: Studies addressing questions relating to Level 0 of the pyramid

Main heading	Lifestyle								Information	Combined
Sub-heading	Diet							Fluids	Educational interventions	
Question addressed	What is the effectiveness of probiotics?	What is the effectiveness of additional dietary fibre?	What are the effects of different milk formula in infants?	What is the effect of a cow's milk-free diet?	What is the effectiveness of sugars (brown sugar, figs syrup, black sugar molasses)?	What are the effects of selenium supplements?	What is the effectiveness of other / alternative dietary intake?	What is the effect of fluid intake?	What are the effects of educational interventions (delivered in addition to routine care)?	What are the effects of combined dietary and behavioural interventions?
Systematic reviews (n=3)	<i>Harris 2019</i> ¹⁰⁵	<i>Piccoli de Mello 2018</i> ¹⁰⁶								
RCTs to be added to systematic reviews (n=9)	Kubota 2020 ¹¹⁸ Sanctuary 2019 ¹²⁴ Chao 2017 ¹¹³	Closa-Monasterolo 2017 ¹¹⁴ Basturk 2017 ¹³⁵ Cassettari 2019 ¹¹¹ Aulia 2016 ¹⁰⁷ Mahdavi 2017 ¹³⁶								

RCT (n=15)			Bongers 2007 ¹⁰⁹ Chao 2007 ¹¹²	Mohammadi -Bourkheili 2021 ¹¹⁰ Dehghani 2012 ¹¹⁵ Iacono 1998 ¹¹⁹	Tajik 2018 ¹²⁶ Dehghani 2019 ¹¹⁶	Tanjung 2016 ¹²⁷	Hassanein 2021 ¹¹⁷ Stepurina 2018 Modaresi Saryazdi 2013*	Young 1998 ¹³⁰	Ritterband 2003 ¹²² Ritterband 2013 ¹²³ Tayag-Lacsina 2019 ¹²⁸ *	
Non-randomised studies			Xinias 2018 ¹²⁹		Beleli 2015 ¹⁰⁸					
Cohort studies			Savino 2003 ¹³⁴ Infante Pina 2008 ¹³³ Infante 2011 ¹³²	Iacono 1995 ¹³¹						
Other primary study										Mazzoni 2017 ¹²⁰

* - published abstract only. Red = high ROB (serious concerns), Amber = Moderate ROB (moderate concerns), Green = Low ROB (no or minor concerns), RCT=Randomized controlled trial.

Table 9: Judgement of certainty in evidence and summary of findings relating to each research question

Question	Relevant studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Judgement of certainty in evidence	Summary of findings
What are the effects of probiotics?	Harris 2019 ¹⁰⁵ systematic review, with addition of data from 2 new RCTs. (3 further trials not able to be combined)	Downgrade once as some studies were at high risk of bias	No downgrade – consistent findings	No downgrade – directness increased with addition of new trial data	No downgrade	No downgrade	MODERATE	Probiotics are not more beneficial than control at improving outcomes in children with constipation, but there is no suggestion that probiotics are not safe.
What is the effectiveness of additional dietary fibre?	Piccoli de Mello 2018 ¹⁰⁶ systematic review, with addition of data from one RCT. (4 further RCTs not able to be combined)	Downgrade once as some studies were at high risk of bias	No downgrade	No downgrade	Downgrade once for heterogeneity	Downgrade once – poor reporting meant some studies could not be incorporated in meta-analysis	VERY LOW	Additional dietary fibre is not more beneficial than control or laxatives.
What are the effects of different milk formula in infants?	Bongers 2007 ¹⁰⁹ , Chao 2007 ¹¹² - RCTs. Xiniias 2018 ¹²⁹ – non-randomised study. Savino 2003 ¹³⁴ , Infante	Downgrade as studies have methodical limitations	No downgrade	Downgrade twice – different milk formula, and different populations studied	Downgrade once – lack of results data presented	Downgrade once – unclear if all measured outcomes are reported	INSUFFICIENT EVIDENCE	There is insufficient evidence on which to reach generalised conclusions about the relative effect of different milk formula.

	Pina 2008 ¹³³ , Infante 2011 ¹³² – cohort studies.							Individual studies do demonstrate some benefits, supporting the need for high quality randomised studies.
What is the effect of a cow's milk-free diet?	Mohammadi Bourkheili 2021 ¹¹⁰ , Deghani 2012 ¹¹⁵ , Iacono 1998 ¹¹⁹ – RCTs. Iacono 1995 ¹³¹ – cohort study	Downgrade once as studies had high/unclear ROB	No downgrade – consistent findings	Downgrade once – difference in studies; some gave intervention in combination with laxatives, others did not	No downgrade – no concerns	No downgrade – no concerns	LOW	There is low certainty that a trial of cow's milk free diet may be beneficial to outcomes, in children for whom laxatives have been unsuccessful. Note: Evidence from studies which included participants who had a diagnosis of cows milk allergy were excluded from this review; this evidence will be important to decisions relating to exclusion of cows milk from diet.

What is the effectiveness of sugars (brown sugar, figs syrup, black sugar molasses)?	Tajik 2018 ¹²⁶ , Deghani 2019 ¹¹⁶ – RCTs. Beleli 2015 ¹⁰⁸ – non-randomised study	Downgrade once as studies had high/unclear ROB for most domains	No downgrade – consistent findings	Downgrade twice – different types of intervention, different adjuncts	No downgrade – no concerns	No downgrade – no concerns	INSUFFICIENT EVIDENCE	There is insufficient evidence on which to reach generalised conclusions about the relative effect of sugars. Individual studies do demonstrate some benefits, supporting the need for high quality randomised studies.
What are the effects of selenium supplements?	<u>RCTs:</u> Tanjung 2016 ¹²⁷	Downgrade once as ROB uncertain for several domains.	Downgrade once as proportion of children with constipation varies from reported prevalence in other populations.	No downgrade	Downgrade once as lack of detail about method of grading outcomes.	No downgrade	VERY LOW	There is very low certainty that selenium supplements may improve outcomes of defecation frequency, stool consistency and abdominal pain.
What is the effectiveness of other / alternative dietary intake?	Hassanein 2021 ¹¹⁷ Stepurina 2018 ¹²⁵ Modaresi Saryazdi 2013 ¹²¹ - RCTs	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	INSUFFICIENT EVIDENCE	There are 3 RCTs, one which is reported only as an abstract, which have investigated a range of alternative dietary intakes, including oral

								magnesium sulfate, magnesium-containing mineral water and paraffin oil. There is insufficient evidence relating to either of these interventions to support generalised conclusions.
What is the effect of fluid intake on constipation?	Young 1998 ¹³⁰ - RCT	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	INSUFFICIENT EVIDENCE	There is insufficient evidence to support any routine change in fluid intake for children with constipation.
What are the effects of educational interventions (delivered in addition to routine care)?	Ritterband 2003 ¹²² , Ritterband 2013 ¹²³ , Tayag-Lacsina 2019 ¹²⁸ - RCTs.	Downgrade once as studies had high/unclear ROB	No downgrade – consistent findings	Downgrade once – 2 studies focus on an internet intervention in children with encopresis, while 1 focuses on a written information leaflet for children with chronic constipation.	Downgrade once – lack of results data presented	Downgrade once – unclear if all measured outcomes are reported.	VERY LOW	There is some limited evidence that educational interventions – particularly web-based interventions focused on education around toilet training – may have a beneficial effect on bowel movements (including frequency, consistency and

								incontinence).
What is the effect of combined dietary and behavioural interventions?	Mazzoni 2017 ¹²⁰ – non randomised study. .	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	INSUFFICIENT EVIDENCE	There is insufficient evidence to support generalised conclusions relating to combined dietary and behavioural interventions.

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