Management of childhood functional constipation in primary care

Jojanneke J.G.T. van Summeren

Management of childhood functional constipation in primary care

Jojanneke J.G.T. van Summeren

Cover & Lay-out: Arnoud Dagelet & Pepijn Koning
Printing: Ridderprint, the Netherlands

The research described in this thesis is financially supported by the Dutch Organization for Health and Development (ZonMw) and the P.W. Boer Foundation and is gratefuly acknowledged.

ZonMw

Financial support for the publication of this thesis, provided by the Research Institute SHARE (School of HeAlth Research), University of Groningen and University Medical Centre Groningen (UMCG), is gratefully acknowledged.

rijksuniversiteit groningen

umcg

rijksuniversiteit
groningen

Management of childhood functional constipation in primary care

Proefschrift

ter verkrijging van de graad van doctor aan de
Rijksuniversiteit Groningen
op gezag van de
rector magnificus prof. dr. C. Wijmenga
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

maandag 9 mei 2022 om 14.30 uur

door

Jojanneke Johanna Geertruida Theodora van Summeren

geboren op 20 mei 1989
te Grubbenvorst

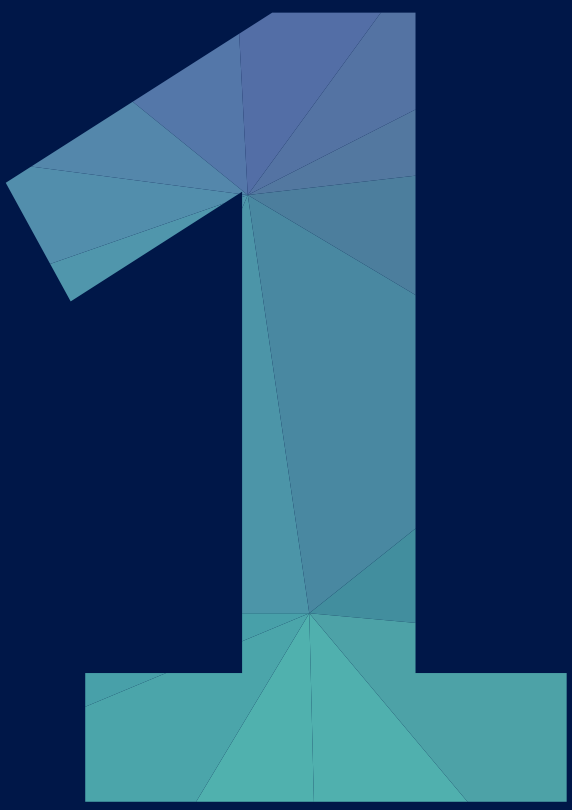
Promotor
Prof. dr. M.Y. Berger

Copromotoren
Dr. J.H. Dekker
Dr. G.A. Holtman

Beoordleingscommissie
Prof. dr. M.A. Benninga
Prof. dr. A. Vermandel
Prof. dr. N.D. Scherpbier-de Haan

Paranimfen
Feikje Groenhof
Petra Santing

Contents



Chapter 1

General introduction

General introduction

Functional constipation (FC) is constipation for which there is no organic explanation. It is a very common condition in children and can have a major impact on the quality of life.[1] Children with FC may have disturbing and embarrassing symptoms, for example fecal incontinence resulting in dirty pants at school.[2-4] They are more likely than their peers to suffer from low self-esteem and experience bullying and this negatively affects their quality of life and that of their families.[5-9] The long-term nature and the impact of symptoms associated with FC are often underestimated by both the child, the parent(s) and medical professionals.[1,10,11] Despite treatment, 50% of the children are still struggling with symptoms after 6-12 months of treatment, and 25% have symptoms of FC up until adulthood.[11,12]

Treatment with laxatives, the most commonly used treatment approach, contributes to the reduction of FC symptoms, however, it does not address the underlying multifactorial etiology of FC which is believed to be a complex interaction between physiologic, psychological, social, and behavioral factors.[4,13] In addition, for many children and their parents it is difficult to adhere to the recommended dose and duration of laxative treatment.[13-16] In order to treat FC in children more effectively, treatment should focus not only on the reduction of symptoms but also on one or more of the assumed pathophysiological mechanisms. Indeed, current evidence suggests that treating early in the disease process might be more effective at achieving treatment success, and also in preventing chronicity. As such, it is important to perform a study focusing on one of those pathophysiological mechanisms in primary care.[17]

Childhood functional constipation

Definition and Epidemiology

In over 90% of the children with constipation no underlying organic or metabolic cause of the constipation is diagnosed and the symptoms are referred to as "functional".[18] Childhood functional constipation (FC) is characterized by symptoms such as abdominal pain, painful bowel movements, large stools, and fecal incontinence.[4,19,20] FC is a common problem in children worldwide, with prevalence ranging between 0.7 and 29.6%, depending on the population studied and the definition of FC.[1] Although FC is a common problem, it is often not recognized by children, parents and clinicians, and therefore not all children (and their parents) seek and receive medical help for FC related symptoms.[10] In general practice, the one-year prevalence of constipation in children, aged 4-17 years, is 34.5 per 1000 children, which means that a full-time general practitioner (GP) in the Netherlands sees around 11 children aged 4-17 years with FC each year.[21,22] For pediatricians and pediatric gastroenterologists, respectively 3-5% and 25% of the visits are related to FC.[23]

The prognosis of children with FC is not favorable, with a long duration of symptoms in many children.[11,12] At the moment, we cannot predict which children are at risk for developing long-term symptoms.[11] Children often tend to downplay their condition and to minimize the severity of their symptoms out of shame. In addition, clinicians and parents do not actively monitor children with FC for persistence or recurrence of symptoms. This has the effect that many children with FC suffer in silence, and so miss the opportunity to get help and run the risk of developing chronic symptoms.

Multifactorial etiology

The etiology of FC in children is multifactorial, involving age, lifestyle factors, psychological factors, behavioral factors, pelvic floor function, gastrointestinal motility and genetic factors.[4,24] In children from 4 years onwards stool-withholding behavior is often thought to play a key role in the pathophysiology of childhood FC.[4] Children often end up in a vicious circle: stool withholding results in stools that become harder owing to water absorption by the colonic mucosa, which leads to a large fecal mass that is difficult to evacuate, resulting in painful defecation, and as a consequence more stool withholding behavior etc. During bowel movements the pelvic floor and abdominal muscles have to contract and relax in a coordinated manner. In many children with FC it is thought that this process has been disrupted, resulting in dyssynergic defecation. These children with dyssynergic defecation appear to contract their pelvic floor muscles, either consciously or unconsciously, and fail to relax the external anal sphincter during bowel movements.[25] In addition, they may have a reduced trunk stability which is needed to achieve the required posture and to build up the intra-abdominal pressure required for defecation.[25,26] In addition, factors like drinking too little, insufficient fiber intake and insufficient physical activity may play a role in the etiology of FC.

FC in children is often associated with lower urinary tract symptoms including urinary incontinence. The exact pathophysiology of this co-occurrence ("bladder-bowel dysfunction") is not yet completely understood.[3,27-29] But it is recommended to ask for bladder problems in children with FC and vice-versa.

Diagnostic criteria

The diagnosis of functional constipation is based on a combination of symptoms presented during medical history and physical examination and the lack of an explanation of these symptoms by another medical condition.[20,30,31] To diagnose FC a group of experts defined the Rome I criteria based on clinical experience and review of the literature in 1994.[32] These criteria were revised in 1999 (Rome II), 2006 (Rome III) and 2016 (Rome IV).[17,20,33] Since Rome II, a different set of criteria is defined for adults, and children and adolescents. Over the

years, no major changes have been made for the diagnosis of FC in children and adolescents, only the duration criterion has been changed: children need to fulfill the diagnostic criteria for at least 1 month (Rome IV) instead of 2 (Rome III) or 3 (Rome II) months.[20] This duration criterion was changed because the literature suggests that the longer the FC goes undiagnosed, the less successful the treatment is.[17] The Dutch guideline for general practitioners on constipation has adopted the Rome criteria, with the exception of the time criterion, arguing that acute symptoms should also be treated and that a delayed start of the treatment might negatively influence the prognosis.[30,31] The criteria for diagnosing FC in children from 4 years of age are summarized in Table 1.

Impact of functional constipation

Children with FC are more likely to experience feelings of shame and low self-esteem, and are more often confronted with bullying compared to their peers.[3] Indeed, FC has a major impact on the quality of life (QoL) of children, with the largest influence on the emotional and social aspects of the QoL.[5-7,9,34] FC also has a significant impact on the family of the child, in

Table 1. Criteria for diagnosing functional constipation in children with a developmental age of ≥4 years according to the Rome II[33] Rome III[17], Rome IV[20] and Dutch guideline for GPs[31]

All three the guidelines include the following:
A child has to fulfill ≥2 of the criteria:

- <3 defecations in the toilet per week
- ≥1 episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools, which may obstruct the toilet

Differences between criteria for FC:

Rome II	Rome III	Rome IV	Dutch Guideline for GPs
• Symptoms exist ≥ 3 months	• Symptoms exist ≥2 months • Functional constipation can only be diagnosed when there is no underlying organic etiology	• Symptoms exists ≥1 month • After appropriate evaluation, the symptoms cannot fully be explained by another medical condition	• No time criterium for the duration of symptoms • Constipation with no evidence of an underlying somatic cause

terms of worrying and social isolation.[8,9] A study showed that 21% of constipated children do not discuss their defecation problems with anyone, even if they have bothersome symptoms several times a week, 65% of children discuss their problems with their family or friends, and only 33% of children (and their parents) consult the GP.[10] This implicates that many children suffer in silence with the risk that their symptoms will become chronic. Children with FC miss more school days than their healthy peers and it also results in the loss of (productive) working days amongst the parents of children with FC.[35]

Childhood FC also has a significant impact on society, reflected in high use and costs of the national health care system.[35,36] In the United States, it is estimated that the direct yearly health care costs for children with FC were 3 times greater than for children without FC.[36] It is known that children with FC and their caregivers often search for alternative and sometimes expensive therapies when the child does not respond to conservative management.

Management of childhood functional constipation in primary care

In the Netherlands, the GP is the first clinician that will be consulted when a child experiences symptoms of constipation. After diagnosing the constipation as functional, implying the exclusion of an organic or metabolic underlying cause of the constipation, the guideline for GPs recommends starting with education, dietary advice, and toilet training.[31] This guideline is in accordance with international and secondary care guidelines for FC.[14,30] If symptoms do not improve after two weeks, the next step is the prescription of laxatives.[31] The scientific evidence to support this approach is limited, and GPs often have insufficient time to give proper education, dietary advice and toilet training.[14,37] In addition, the quality of the evidence on the effectiveness of the prescribed laxatives is low and adherence to the advised dosage and (the long) duration of treatment is problematic.[13-16]

Although the multifactorial nature of the condition is acknowledged in the guidelines, it is difficult for the GP (and other busy medical professionals) to pay sufficient attention to education, dietary advice and toilet training of children with FC.[38] Nor do parents always have sufficient time to help their child. GPs can advise children (and/or the parents) to visit a website of the Dutch society of GPs (www.thuisarts.nl) with additional information on FC in children and instructions to help reduce FC related symptoms.[39] In recent years, instructional videos with additional information about constipation and toilet training have also been made available via this website. However, one of the problems with FC is that children and parents do often underestimate the symptoms, are too embarrassed to talk about the symptoms, or do not even recognize the symptoms at all.[10,38] This has a negative impact on the adherence to the recommended treatment and results in a delay in medical help-seeking behavior.[15] The combination of these factors might contribute to treatment

failure in primary care which leads to unnecessary referral to pediatricians in hospitals specialized in defecation problems in children (in Dutch Poeppoli's).

Role of physiotherapy in the treatment of constipation in children

As outlined above, a vicious circle of stool withholding, painful defecation and large stools that are difficult to evacuate, might result in dyssynergic defecation with contraction instead of relaxation of the pelvic floor muscles during defecation.[40] In addition, poor coordination of abdominal and pelvic floor muscles and insufficient core stability are thought to play a role. A treatment involving re-education of the muscles which are important in the defecation process in combination with comprehensive education and attention to other aspects related to the multifactorial etiology of the condition (e.g. nutrition, physical activity, psychosocial factors) might be an effective strategy for FC, more effective than conventional treatment alone. Such a treatment is available in the Netherlands: in primary care it is mainly the domain of specialist physiotherapists, with a master in pediatric or pelvic physiotherapy and additional education in childhood bladder and bowel problems. Physiotherapy is also used in the hospital setting, and a few studies, with a small population, have shown promising results in this setting.[41-43] Physiotherapy treatment is relatively cheap and available in primary care whether or not after referral by the GP. However, the effectiveness of adding physiotherapy for FC to conventional treatment is not studied in primary care. Since physiotherapy is directed at one of the causes of the constipation namely the dyssynergic defecation, but also includes other factors related to the multifactorial etiology that might play a role, it is hypothesized that the chronicity of the symptoms can be prevented by adding physiotherapy to conventional treatment, especially if the treatment starts early in the disease process.

Thesis aim and rationale

FC is a common disorder in children, with symptoms that they generally experience as being embarrassing and which have a great impact on the QoL of the child and the family. Despite conventional treatment, symptoms may persist for many years, even up until adulthood. Additional interventions are needed, which focus more on the multifactorial etiology of the condition. Given the potentially important role of dyssynergic defecation in FC, a treatment that in any case also includes rehabilitation of the pelvic floor and abdominal muscles, is worth studying.

Therefore, we designed the BOKI trial. BOKI stands for Treatment of Constipation in children (in Dutch: Behandeling van Obstipatie in KInderen). In this pragmatic randomized controlled trial in primary care, we have evaluated whether adding physiotherapy to conventional treatment by the GP is an effective and cost-effective treatment strategy for children, aged 4 to 17 years, with FC compared to conventional treatment alone.

Thesis outline:

Chapter 2 describes the final study design of the BOKi randomized controlled trial, including a process evaluation of the adaptations to the original study design to overcome recruitment problems. In **Chapter 3** the results of the evaluation of the effectiveness of physiotherapy added to conventional treatment in primary care are presented in terms of treatment success defined as "absence of FC symptoms according to the Rome III criteria and no laxative use" and "absence of FC symptoms according to the Rome III criteria irrespective of laxative use", quality of life and global perceived effect. In **Chapter 4** the results of the cost-effectiveness analyses performed alongside the BOKi trial are reported. The cost-effectiveness analyses are performed from a societal perspective with the two previously described definitions of treatment success after 8 months as the health outcome measure.

There is substantial debate in the literature regarding the most appropriate respondent for assessing children's health related quality of life (HRQoL): the child self or the parent(s). In **Chapter 5** we have used the baseline data collected in the BOKi trial to examine the parent-child agreement on HRQoL in children aged 8-17 years. In addition, we have investigated whether this agreement was associated with age or gender of the child. Co-occurrence of bladder symptoms and functional constipation is often reported, but the actual extent of the problem is unknown. It is thought that this co-occurrence can be explained because the bowel and bladder share a common pathway. In **Chapter 6** we present the results of a systematic review of studies on the prevalence of bladder symptoms in children with FC. In addition, we have performed a meta-analysis to compare the prevalence of bladder symptoms in children with and without FC.

In **Chapter 7** the main findings of this thesis are summarized, and we reflect on the methodological considerations, clinical implications of the findings, recommendations for the management of children with FC, implications for clinical guidelines and future perspectives for the management of children with FC in primary care.

References

1. Koppen IJ, Vriesman MH, Saps M, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. The Journal of pediatrics. 2018;198:121-130. e126.
2. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best practice & research Clinical gastroenterology. 2011;25(1):3-18.
3. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem. World journal of gastroenterology. 2016;22(30):6864.
4. Vriesman MH, Koppen IJ, Camilleri M, Di Lorenzo C, Benninga MA. Management of functional constipation in children and adults. Nature Reviews Gastroenterology & Hepatology. 2020;17(1):21-39.
5. Kovacic K, Sood MR, Mugie S, et al. A multicenter study on childhood constipation and fecal incontinence: effects on quality of life. The Journal of pediatrics. 2015;166(6):1482-1487. e1481.
6. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Alimentary pharmacology & therapeutics. 2010;31(9):938-949.
7. Rajindrajith S, Devanarayana NM, Weerasooriya L, Hathagoda W, Benninga MA. Quality of life and somatic symptoms in children with constipation: a school-based study. The Journal of pediatrics. 2013;163(4):1069-1072. e1061.
8. Kaugars AS, Silverman A, Kinservik M, et al. Families' perspectives on the effect of constipation and fecal incontinence on quality of life. Journal of pediatric gastroenterology and nutrition. 2010;51(6):747-752.
9. Vriesman MH, Rajindrajith S, Koppen IJ, et al. Quality of life in children with functional constipation: a systematic review and meta-analysis. The Journal of pediatrics. 2019;214:141-150.
10. Timmerman ME, Trzpis M, Broens PM. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. European journal of pediatrics. 2019;178(1):33-39.
11. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. Journal of pediatric gastroenterology and nutrition. 2010;50(3):256-268.
12. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics. 2010;126(1):e156-e162.

13. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database of Systematic Reviews. 2016(8).
14. Tabbers M, DiLorenzo C, Berger M, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. Journal of pediatric gastroenterology and nutrition. 2014;58(2):258-274.
15. Koppen IJN, van Wassenaer EA, Barendsen RW, Brand PL, Benninga MA. Adherence to polyethylene glycol treatment in children with functional constipation is associated with parental illness perceptions, satisfaction with treatment, and perceived treatment convenience. The Journal of pediatrics. 2018;199:132-139. e131.
16. Steiner SA, Torres MR, Penna FJ, et al. Chronic functional constipation in children: adherence and factors associated with drug treatment. Journal of Pediatric Gastroenterology and Nutrition. 2014;58(5):598-602.
17. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527-1537.
18. Loening-Baucke V. Chronic constipation in children. Gastroenterology. 1993;105(5):1557-1564.
19. Burgers R, de Jong TP, Visser M, Di Lorenzo C, Dijkgraaf MG, Benninga MA. Functional defecation disorders in children with lower urinary tract symptoms. The Journal of urology. 2013;189(5):1886-1891.
20. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1456-1468. e1452.
21. Nielen M, Hek K. Cijfers huisartsen - Patiëntkenmerken. https://www.nivel.nl/nl/nivel-zorgregistraties-eerste-lijn/patientkenmerken. Accessed 13-11-2021, 2021.
22. Hommes N. Een kijk in de huisartsenpraktijk: De behandeling van kinderen met obstipatie [Master scriptie]. [Submitted 2013, Sep 10]
23. Baker SS, Liptak GS, Colletti RB, et al. Constipation in infants and children: evaluation and treatment. Journal of pediatric gastroenterology and nutrition. 1999;29(5):612-626.
24. van Engelenburg–van Lonkhuyzen ML, Bols EM, Benninga M, Groen LA, Chase J, de Bie R. Physiotherapy interventions for functional bladder and bowel dysfunctions in neurologically normal and otherwise healthy children. Cochrane Database of Systematic Reviews. 2016(11).
25. Loening-Baucke V, Cruikshank B, Savage C. Defecation dynamics and behavior profiles in encopretic children. Pediatrics. 1987;80(5):672-679.
26. Benninga M, Voskuijl W, Akkerhuis G, Taminiau J, Büller H. Colonic transit times

and behaviour profiles in children with defecation disorders. Archives of disease in childhood. 2004;89(1):13-16.
27. Van Den Berg MM, Benninga M, Di Lorenzo C. Epidemiology of childhood constipation: a systematic review. Official journal of the American College of Gastroenterology| ACG. 2006;101(10):2401-2409.
28. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourology and urodynamics. 2016;35(4):471-481.
29. Dos Santos J, Lopes RI, Koyle MA. Bladder and bowel dysfunction in children: an update on the diagnosis and treatment of a common, but underdiagnosed pediatric problem. Canadian Urological Association Journal. 2017;11(1-2Suppl1):S64.
30. Nederlandse Vereniging voor Kindergeneeskudne, Nederlands Huisarts Genootschap. Richtlijn obstipatie bij kinderen van 0 tot 18 jaar [Internet]. [cited 2021, Nov 19]. Available from: https://richtlijnendatabase.nl/richtlijn/obstipatie_bij_kinderen_van_0_tot_18_jaar/ obstipatie_-_startpagina.html
31. Nederlands Huisartsen Genootschap. NHG standard obstipatie [Internet]. [cited 2021, Nov 19]. Available from: https://richtlijnen.nhg.org/standaarden/obstipatie#volledige-tekst
32. Drossman DA, Richter JE, Talley NJ. The functional gastrointestinal disorders: diagnosis, pathophysiology and treatment. McLean (VA): Degnon Associates. 1994.
33. Rasquin-Weber A, Hyman P, Cucchiara S, et al. Childhood functional gastrointestinal disorders. Gut. 1999;45(suppl 2):II60-II68.
34. Varni JW, Bendo CB, Nurko S, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. The Journal of pediatrics. 2015;166(1):85-90.e82.
35. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. The Journal of pediatrics. 2009;154(2):258-262.
36. Choung RS, Shah ND, Chitkara D, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. J Pediatr Gastroenterol Nutr. 2011;52(1):47-54.
37. Pijpers MA, Tabbers M, Benninga MA, Berger MY. Currently recommended treatments ofchildhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Archives of disease in childhood. 2009;94(2):117-131.
38. Thompson AP, Wine E, MacDonald SE, Campbell A, Scott SD. Parents' Experiences and Information Needs While Caring for a Child With Functional Constipation: A Systematic

Review. Clin Pediatr (Phila). 2021;60(3):154-169.
39. Thuisarts.nl. Mijn kind heeft last van verstopping [Internet]. [cited 2021, Nov 19]. Available from: https://www.thuisarts.nl/verstopping/mijn-kind-heeft-last-van-verstopping
40. Makosiej R, Makosiej A, Bossowski A, et al. Dyssynergic Defecation and Anal Sphincter Disorders in Children in High-Resolution Anorectal Manometry Investigation. Journal of Pediatric Gastroenterology and Nutrition. 2020;71(4):484-490.
41. Silva CA, Motta ME. The use of abdominal muscle training, breathing exercises and abdominal massage to treat paediatric chronic functional constipation. Colorectal Dis. 2013;15(5):e250-255.
42. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, Verwijs WA, de Bie RA. Effectiveness of Pelvic Physiotherapy in Children With Functional Constipation Compared With Standard Medical Care. Gastroenterology. 2017;152(1):82-91.
43. van Summeren J, Dekker J, Berger M. Pelvic Physiotherapy in Children With Functional Constipation: Promising But More Research Needed. Gastroenterology. 2017;152(8):2080-2081.

2

Chapter 2

Physiotherapy plus conventional treatment versus conventional treatment only in the treatment of functional constipation in children: design of a randomized controlled trial and cost-effectiveness study in primary care

Jojanneke J. G. T. van Summeren, Gea A. Holtman,
Yvonne Lisman-van Leeuwen, Lisa E. A. M. Louer,
Alice H. C. van Ulsen-Rust, Karin M. Vermeulen,
Boudewijn J. Kollen, Janny H. Dekker and Marjolein Y. Berger

BMC pediatrics 2018; 18: 249

Abstract

Background

Our aim was to design a study to evaluate the effectiveness and cost-effectiveness of adding physiotherapy to conventional treatment for children with functional constipation in primary care. Physiotherapy is focusing on improving the coordination between the pelvic floor and abdominal musculature during bowel movement, while conventional treatment is mainly focusing on symptomatic relief of symptoms, therefore, we expect the effects of physiotherapy will be more sustainable than the effects of conventional treatment. In this paper we describe the final study design and how the design was adapted, to overcome recruitment problems.

Methods

We designed a randomized controlled trial of children aged 4–17 years with functional constipation diagnosed by a general practitioner or pediatrician. Children in the intervention group received physiotherapy plus conventional treatment, and those in the control group received conventional treatment only. Follow-up measurements took place at 4 and 8 months. The primary outcome was treatment success defined according to the Rome-III criteria as the absence of functional constipation, with no laxative use. Secondary outcomes were absence of functional constipation irrespective of laxative use, quality of life, global perceived effect, and costs. Children were recruited from September 2014 to February 2017. Initially, we aimed to include children with recent symptom onset. However, in the first phase of enrollment we were confronted with an unforeseen recruitment problem: many children and their parents refused randomization because physiotherapy was considered too burdensome for the stage of disease. Therefore, we decided to also include children with a longer duration of symptoms. In total 134 children were included.

Discussion

The target number of participants is achieved. Therefore, the results may change thinking about the management of functional constipation in children.

Background

Functional constipation (FC) is a common problem in children.[1] Its etiology is multifactorial, involving age, behavior, pelvic floor function, and gastrointestinal motility. Conventional treatment includes education, dietary advice, toilet training, and laxatives.[2,3] However, despite this multifaceted approach, 50% of children still experience FC after 6–12 months' treatment with laxatives and 25% have symptoms that persist into adulthood.[4,5] Therewith FC has not only a major impact on the quality of life of both children and their families but also increases healthcare costs significantly.[6,7,8]

The pelvic floor and abdominal muscles contract and relax in a coordinated manner during bowel movements, and dysfunction of this interaction could be important in the onset and maintenance of FC.[9] Children with FC, either consciously or unconsciously, appear to strain their pelvic floor muscles and fail to relax the external anal sphincter during bowel movements.[10,11] In addition, reduced trunk stability may preclude achievement of the posture and intra-abdominal pressure required for defecation.[10,12] Physiotherapy for FC focuses on improving this coordination between the abdominal and pelvic floor musculature.[9] To date, two small clinical trials in specialist care have shown promising results for the effects of physiotherapy in children with FC.[13,14] Physiotherapy is expected to give optimal results in children with recent symptom onset.[4] Therefore, it could be particularly effective in children presenting to primary care.

We aimed to design a randomized controlled trial to evaluate the effectiveness and cost-effectiveness of physiotherapy plus conventional treatment in comparison to conventional treatment alone for children aged 4–17 years presenting with FC in primary care. We encountered problems in the recruitment of participants that led us to change the original criteria for participant selection. In this paper we therefore start with presenting our final study design. Thereafter, we describe the process of recruiting participants, including the changes implemented in the original study design. Lastly, we evaluate the representativeness of our study population by comparing characteristics of children that participated and refused to participate in this trial.

Methods

Design

We designed a randomized controlled trial that had a follow-up period of 8 months, and wherein children were included between September 2014 and March 2017. The trial was

approved by the Medical Ethical Board of the University Medical Center of Groningen (METC2013/331) and was registered in the Netherlands Trial Register (NTR4797). Before enrollment we obtained written informed consent from all parent(s). In addition, children aged ≥12 years provided written informed consent themselves.

Participants

Eligibility criteria

Children were eligible for inclusion if aged 4–17 years and diagnosed with FC by a general practitioner (GP) or general pediatrician. Specifically, children were required to have experienced FC symptoms or to have used laxatives in the 4 weeks before enrollment. Children under the age of 4 years were considered too young to undergo physiotherapy.[9] The exclusion criteria were psychopathology affecting protocol adherence, severe disease (physician determined), and physiotherapy or urotherapy for constipation in the past 3 years (Figure 1).

Patient recruitment

We recruited all children (aged 4–17 years) presenting to general practices or who were newly referred to pediatric outpatient departments with a diagnosis of FC. During the first consultation for FC symptoms, parents and children were informed about this study by their treating physician (incident cases). In addition, any children with a known diagnosis of FC and who had consulted their GP in the past 12 months for this diagnosis were sent a leaflet explaining the study (prevalent cases). Children or their parents (depending on the child's age) were asked to complete a short questionnaire supplied with the leaflet, detailing whether the child had experienced symptoms of FC or used laxatives in the past 4 weeks. Once completed, they were asked to return the questionnaire.

Interventions

Control group: conventional treatment only

Children in the control group received conventional treatment. No restrictions or recommendations were given to the physicians regarding treatment. However, education, dietary advice, toilet training, and when indicated, laxative prescribing were permitted based on appropriate guidance.[2,3]

Intervention group: physiotherapy plus conventional treatment

Children in the intervention group received physiotherapy in addition to conventional treatment. Physiotherapy consisted of a maximum of nine half-hour sessions carried out by specialist physiotherapists, and ended if the physiotherapist considered that treatment was successful or that no more improvement was expected. The physiotherapists were trained

to master's degree level in pediatric or pelvic physiotherapy, and had received postgraduate education in the treatment of bladder and bowel dysfunction in children. The patient-tailored structured treatment program used in this study was developed in cooperation with experienced specialist physiotherapists and approved by all participating specialist physiotherapists before the study. The physiotherapist tailored the treatment program to the individual patient. For each patient and session, the physiotherapists recorded on a structured form the treatment options used to reach the six goals.

In young children, physiotherapy focused on the child and his or her parent(s), while in older children, the focus was mainly on the child. All exercises, materials, and methods were presented in a manner appropriate to the child's developmental age and locomotor skills. For the patient-tailored structured treatment program used in this study, the six goals were: 1) improving the knowledge about defecation, and the role that the child and/or parent might have in the persistence of symptoms; 2) improving toileting behavior and practicing a stable toilet posture; 3) increasing awareness of the sensation of needing to defecate; 4) learning to relax while defecating; 5) learning to breath correctly to generate adequate intra-abdominal pressure for defecation; and 6) teaching effective straining for defecation. Biofeedback and electrotherapy were not allowed in this study because there is insufficient evidence of their efficacy in children with FC and because we considered these therapies too invasive for treatment of children presenting to primary care.[15]

Randomization and blinding

Children were randomly allocated in a 1:1 ratio to the two treatment groups, using a computer-generated randomization list with random block sizes. Randomization was stratified into those aged 4–8 years and those aged 9–17 years. The randomization list was maintained by a researcher who was not involved in the study and had no access to the allocation site.

Children, parents, physicians, and physiotherapists could not be blinded to the intervention. The investigator was blinded to the assigned study group during data entry and statistical analyses.

Outcomes

The primary outcome was treatment success, defined according to the Rome-III criteria as the absence of FC without laxative use (see Table 1 for the Rome-III criteria used to define FC).[16] Thus, a successfully treated child was required to fulfill none or one of the six Rome-III criteria. Other secondary outcomes were absence of FC according to the Rome-III criteria irrespective of laxative use, quality of life, global perceived treatment effect, and costs.

Measurements

Figure 1 gives an overview of the measurement and timing of baseline characteristics and the primary and secondary outcome parameters; follow-up measurements took place after 4 and 8 months. We collected the following data at baseline: age, gender, symptom duration, age at symptom onset, symptom chronicity, and whether lower urinary tract symptoms were present. Symptom chronicity was defined as continuous or regular laxative use (≥3 periods) in the 12 months before inclusion.

Measurement of the primary outcome

The presence of FC was assessed with a Dutch version of the Questionnaire on Pediatric Gastrointestinal Symptoms Rome-III (QPGS-RIII).[16] This standardized questionnaire was used to assess if children have experienced functional gastrointestinal symptoms over the last 2 months. We adapted the questionnaire and evaluated symptoms over a period of 4 weeks. Children completed the questionnaire themselves if they were aged 13–17 years,

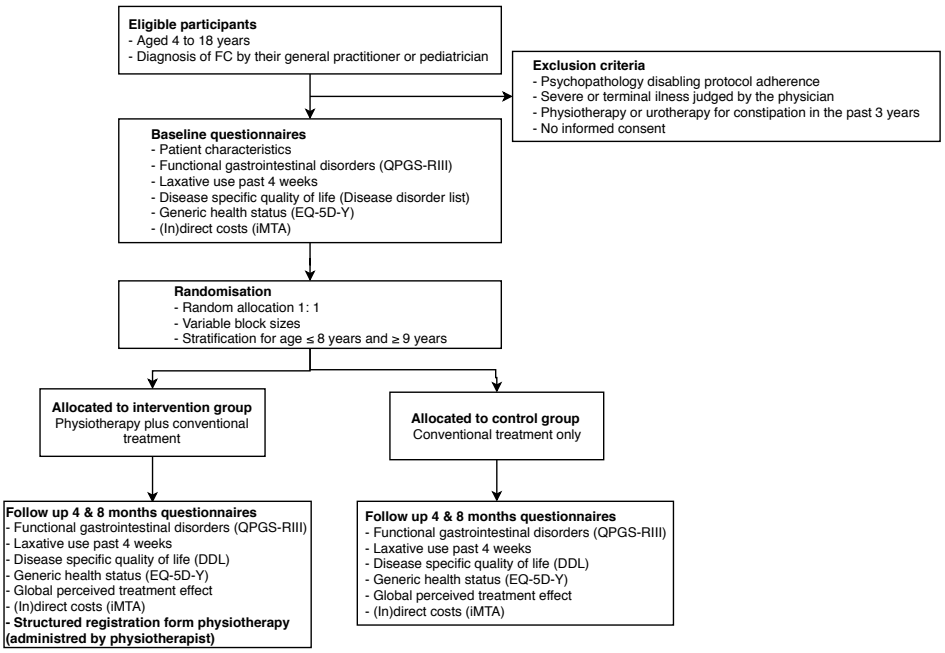


Figure 1. Flowchart of study design: eligibility criteria for participants, planned measurement and timing of baseline characteristics and the primary and secondary outcome measurements. Abbreviations: FC, functional constipation, QPGS-RIII, Questionnaire on Pediatric Gastrointestinal Symptoms Rome-III, EQ-5D-Y, EuroQol-5-dimensions-youth, iMTA, Institute of Medical Technology Assessment Medical Consumption Questionnaire, DDL, Defecation Disorder List

but parents completed the questionnaire if their child was aged 4–12 years. In addition, parents answered the question "Did your child use laxatives in the past four weeks?" (yes or no). If one or more responses were missing for the primary outcome measure, we contacted the child or parent by telephone to obtain an answer.

Table 1. Description of the Rome III criteria for functional constipation[16]

According to the ROME III criteria, a child must have a developmental age of at least 4 years and fulfill two or more of the following criteria, at least two months prior to diagnosisa:
1) two or fewer defecations in the toilet per week,
2) at least one episode of fecal incontinence per week,
3) history of retentive posturing or excessive volitional stool retention at least once a week,
4) history of painful or hard bowel movement at least once a week,
5) presence of a large fecal mass in the rectum at least once a week,
6) history of large diameter stools that may obstruct the toilet at least once a week.

aFor the purpose of this study, patients were eligible for enrollment if symptoms were present for at least one month before diagnosis, rather than two months, which is in agreement with the recently published Rome-IV criteria[27]

Measurement of secondary outcomes

Disease-specific quality of life was measured with the Defecation Disorder List (DDL)[17,18], adapted to include only the emotional and social functioning subdomains. The constipation-related and treatment/intervention subdomains were omitted because it has previously been demonstrated that these have low internal consistency and potentially low validity when used to measure disease-specific quality of life.[17,18] Health status was measured with the EuroQol-5-dimensions-youth (EQ-5D-Y).[19] Proxy report versions of the DDL and EQ5D-Y questionnaires were completed by parents, and children aged ≥8 years also completed child self-reports. The global perceived treatment effect of patients (GPE) was scored by parents and measured with a 9-point Likert-type scale (very much, much, reasonable, and slightly improved; no change; slightly, reasonable, much, and very much worse). When parents reported that the symptoms of their child were improved very much or much we defined the treatment as successful.

Healthcare consumption related to FC, such as GP or pediatrician visits, drug treatment, and parental productivity loss, were measured with versions of the Institute of Medical Technology Assessment Medical Consumption Questionnaire (iMTA-MCQ) and the Productivity Costs Questionnaire (iMTA-PCQ), respectively, adjusted for FC.[20,21] Both cost questionnaires were completed by parents only.

If questionnaires were not returned, participants were sent a reminder e-mail after 2 weeks and received a reminder telephone call after 3 weeks.

Sample size

Sample size estimates were based on a systematic literature review showing that after 6 to

12 months of conventional treatment, 50% of the children were free of symptoms without using laxatives.[22] Physiotherapy in one study has been shown to improve outcomes by 30% compared with conventional treatment alone in children with FC referred to pediatric specialist care.[14] However, that study may have overestimated the magnitude of effect because it was small and underpowered.[23] Therefore, we used a more conservative estimate of the difference in treatment success (25%) between the intervention and control group. The sample size was calculated with expected treatment success rates after 6–12 months of 50 and 75% in the conventional and intervention groups, respectively.[14,22] Given an expected loss to follow-up of 10%, we estimated a total sample size of 128 children (alpha 0.05, power 0.80).

Statistical analyses

We will use appropriate descriptive statistics to describe patient characteristics, baseline questionnaire scores, and the proportions of successfully treated children at 4 and 8 months in the intervention and control groups.

We will use multilevel analyses to investigate the longitudinal relationship between the intervention group (physiotherapy plus conventional treatment) and the control group (conventional treatment) with respect to the primary and secondary outcome variables. The applied levels will be repeated measures (that is, time), and patient. We will base our analyses on intention to treat (ITT). The ITT population will consist of all patients who have given informed consent and have been randomly allocated to one of the two treatments, irrespective of whether they received the allocated treatment or not. An additional secondary per protocol analysis (PP) will be conducted for the outcome variable. The PP population will consist of all children randomized in the intervention group receiving at least one physiotherapy session and all children in the control group that had no physiotherapy. Finally, in a sensitivity analysis we will evaluate whether the effect of the intervention is different for children with and without chronic symptoms.

Economic evaluation

A cost-effectiveness analysis is planned. The primary aim will be to estimate the societal costs, and the secondary aim will be to estimate the cost-effectiveness of treatment with physiotherapy plus conventional treatment compared to conventional treatment alone. In addition, we will perform a cost-utility analysis based on EuroQol-defined utilities. The parental version of the EQ5D-Y questionnaire will be used for these evaluations. The cost-effectiveness analyses will then be expressed as incremental cost-effectiveness ratios (ICERs), displaying the extra treatment costs of physiotherapy to gain one extra patient with successful treatment, as compared with conventional care. In turn, cost-utility analyses will

be expressed as incremental cost-utility ratios (ICURs), displaying the extra costs to gain one additional quality-adjusted life year (QALY). Given that the study follow-up was only planned to be 8 months, we will not include discounting of costs and effects. Bootstrap resampling will be performed on the cost and effect pairs to estimate confidence intervals more accurately and to create a cost-effectiveness plane.

Process evaluation of adaptations to the original study design

Criteria for participant eligibility

We had intended to include only those children with FC of recent onset. Therefore, we originally excluded children who were using laxatives or who had used laxatives in the previous 3 months. However, when study enrollment started in September 2014, we were confronted unexpectedly with the fact that many children and parents refused to participate in this trial because they considered the symptoms were not severe enough to justify referral for physiotherapy, which could occur if they consented in randomization. Consequently, many of these patients preferred to opt for laxatives before considering referral to physiotherapy. After recruiting only 20 children over a 12-month period, we decided to expand our eligibility criteria to include also those children who were currently using, or who had used, laxatives in the previous 3 months. This meant that our study population was expanded with children with more advanced FC. Expanding the inclusion criteria also allowed us to include children who had been seen by their GP for FC in the past 12 months, as well as consecutive children newly referred to pediatric outpatient departments. For budgetary reasons, the delay in participant recruitment forced us to shorten the planned follow-up period from 12 months to 8 months. The Medical Ethical Board of the University Medical Center of Groningen approved these changes in study design (METC2013/331).

Sample size calculation

The original sample size calculation was based on conventional treatment being successful in 60% of children consulting their GP for the first time for FC.[24] At that time, no studies had reported on the treatment effects of physiotherapy, and we estimated a 20% difference in treatment success between the intervention and control groups to be relevant.[22] Thus, we expected the treatment under study would be successful in 80% of the children receiving physiotherapy. Given an expected loss to follow-up of 10%, we had calculated that 180 children would be required for the study (alpha 0.05, power 0.80). However, since the original design, a study had been reported on the effectiveness of physiotherapy in childhood FC in a pediatric outpatient department.[14] Therefore, coupled with the changes in study design, we

reconsidered our sample size calculation (see methods section).

Representativeness of the finally selected study population

Children were recruited from 93 general practices (209 GPs) and 5 general pediatric outpatient departments in district hospitals between September 2014 and March 2017. Of the 224 children assessed for eligibility, 213 children were invited by GPs: 44 children with a new diagnosis (incident cases), and 169 children with a diagnosis of FC within the past 12 months (prevalent cases); and 11 newly referred children were invited by pediatricians (Figure 2).

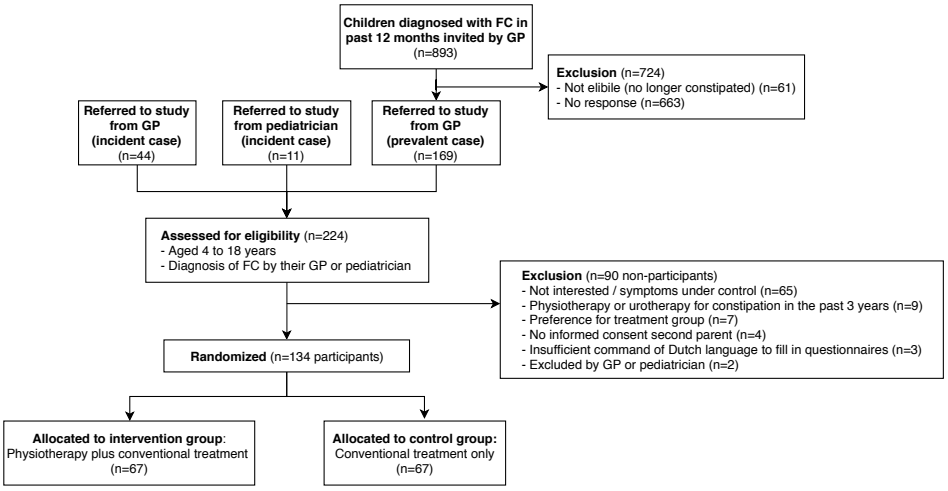


Figure 2. Flowchart of actual participant recruitment and participant flow. Abbreviations: FC, Functional constipation, GP, General practitioner

We compared patient characteristics between children included in the trial (participants, n = 134) and children who refused to participate or who met the exclusion criteria (non-participants, n = 90) (Figure 2 and Table 2). Participants were found to be slightly younger (mean age, 7.5 ± 3.5 years) compared with non-participants (mean age, 8.2 ± 3.8 years), but the boy-to-girl ratio was comparable (Table 2). Among non-participants, symptom chronicity was only assessed in children referred as prevalent cases by their GP for logistical reasons. Comparing chronicity among prevalent cases seems to show that participants more often had chronic symptoms at baseline (65%) compared with non-participants (43%) (Table 2).

Table 2. Characteristics of participants and non-participants

	Participants (n = 134)	Non-participants (n = 90)
Age (mean, SD)	7.5 ± 3.46	8.23 ± 3.80a
Gender (% girls)	61.2	60.0a
Referred to study by:		
- GP (incident case), (n, %)	22 (17%)	22 (24%)
- Pediatrician (incident case), (n, %)	6 (4%)	5 (6%)
- GP (prevalent case), (n, %)	106 (79%)	63 (70%)
Chronicity of symptoms before randomization b, c		
-Yes (n, %)	67 (65%)	16 (43%)
-No (n, %)	36 (35%)	21 (57%)

GP General practitioner, SD standard deviation
a Age and gender were not available of 19 non-participants
b Comparison of chronicity of symptoms between participants and non-participants, was only performed for prevalent cases in whom the question about chronicity was asked (participants n = 103, non-participants n = 37)
c Symptom chronicity was defined as continuous or regular laxative use (≥3 periods) in the 12 months before inclusion

Discussion

Although two small clinical trials have shown that physiotherapy for FC could be a promising treatment for children in specialist care[13,14], we are not aware of any trial evaluating its effectiveness in primary care where most children with FC are diagnosed and treated.[25] The aim of physiotherapy is to improve the coordination between the abdominal and pelvic floor musculature during bowel movement.[9] The strength of physiotherapy is that physical exercises are combined with cognitive and behavioral elements, such as education and toilet training.[26] Treatment guidelines recommend that these cognitive and behavioral elements be discussed by doctors during a consultation.[2,3] However, this might be problematic because GPs focus on symptomatic relief of symptoms. In addition, the consultation time is only 10 min in primary care, which limits the time for proper education, and advices on toilet training.

Initially, we had aimed to assess physiotherapy in children with recent-onset FC, for two main reasons. First, we assume that the long-term prognosis could be more improved if children receive treatment early in the disease process.[4] Second, we think that duration of symptoms and of treatments would be more homogenous in children with recent onset of symptoms. However, we discovered that parents and children could not be motivated for a time-intensive therapy like physiotherapy for symptoms they considered to be temporary and mild. Our subsequent comparison of participants and non-participants confirmed that children were more inclined to participate if they had longer symptom durations and regular laxative use. Therefore, our study will generate results on the effects of physiotherapy for children with more advanced FC than we had originally planned. Specifically, we expect our results to concern those cases where the child or parent have experienced conventional

primary care treatment to be insufficient.

We hypothesized that physiotherapy, by increasing awareness of the abdominal and pelvic floor muscle use during defecation, would have a more sustained effect on outcomes than symptomatic treatment with laxatives. Although we were therefore particularly interested in the long-term effects of physiotherapy, the follow-up duration had to be shortened from 12 to 8 months. However, a follow-up duration of 12 months is probably also too short to evaluate whether the effects of physiotherapy are sustainable. The results of this study will help deciding if it is justified to plan a long term follow-up study.

Clinical impact

We designed the first trial to evaluate the effectiveness of physiotherapy as a first-line treatment for childhood FC in primary care. In total 134 children were included, giving this study sufficient power to lead to promising results. These results may change thinking about the management of functional constipation in children.

References

1. Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. Nat Rev Gastroenterol Hepatol. 2011;8(9):502–11.
2. Nederlandse Vereniging voor Kindergeneeskunde, Nederlands Huisarts Genootschap: Richtlijn obstipatie bij kinderen van 0 tot 18 jaar. 2009. http:// www.nvk.nl/Portals/0/richtlijnen/Obstipatie/Obstipatie%20bij%20kinderen%20van%200%20tot%2018%20jaar%20revisie%202016.pdf
3. National Collaborating Centre for Women's and Children's Health (UK): Constipation in children and youn people: diagnosis and management of idiopathic childhood constipation in primary and secondary care. 2010, https://www.nice.org.uk/guidance/cg99.
4. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics. 2010; 126(1):e156–62.
5. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr. 2010;50(3):256–68.
6. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31(9):938–49.
7. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. J Pediatr. 2009;154(2):258–62.
8. Choung RS, Shah ND, Chitkara D, Branda ME, Van Tilburg MA, Whitehead WE, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. J Pediatr Gastroenterol Nutr. 2011;52(1):47–54.
9. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga M, Groen L, Chase J, de Bie R. Physiotherapy interventions for functional bladder and bowel dysfunctions in neurologically normal and otherwise healthy children. Cochrane Library. 2016;
10. Loening-Baucke V, Cruikshank B, Savage C. Defecation dynamics and behavior profiles in encopretic children. Pediatrics. 1987;80(5):672–9.
11. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, Verwijs WA, de Bie RA. Bladder and bowel dysfunctions in 1748 children referred to pelvic physiotherapy: clinical characteristics and locomotor problems in primary, secondary, and tertiary healthcare settings. Eur J Pediatr. 2017; 176(2):207–16.
12. Chase JW, Stillman BC, Gibb SM, Clarke MC, Robertson VJ, Catto-Smith AG, et al. Trunk strength and mobility changes in children with slow transit constipation. J Gastroenterol Hepatol. 2009;24(12):1876–84.

13. Silva C, Motta M. The use of abdominal muscle training, breathing exercises and abdominal massage to treat paediatric chronic functional constipation. Color Dis. 2013;15(5):e250–5.
14. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, Verwijs WA, de Bie RA. Effectiveness of pelvic physiotherapy in children with functional constipation compared with standard medical care. Gastroenterology. 2017; 152(1):82–91.
15. Brazzelli M, Griffiths PV, Cody JD, Tappin D. Behavioural and cognitive interventions with or without other treatments for the management of faecal incontinence in children. Cochrane Library. 2011;
16. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527–37.
17. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, Grootenhuis MA, Derkx BH, Benninga MA. Health related quality of life in disorders of defecation: the defecation disorder list. Arch Dis Child. 2004;89(12):1124–7.
18. Bongers ME, van Dijk M, Benninga MA, Grootenhuis MA. Health related quality of life in children with constipation-associated fecal incontinence. J Pediatr. 2009;154(5):749–53. e1
19. Wille N, Badia X, Bonsel G, Burström K, Cavrini G, Devlin N, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Qual Life Res. 2010;19(6):875–86.
20. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Handleiding iMTA Productivity Cost Questionnaire (iPCQ). Rotterdam: iMTA, Erasmus Universiteit; 2013.
21. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap MA, Krol M, Severens JL, Brouwer W. iMTA medical consumption questionnaire: handleiding: Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam; 2013.
22. Pijpers MA, Tabbers MM, Benninga MA, Berger MY. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Arch Dis Child. 2009;94(2):117–31.
23. van Summeren J, Dekker J, Berger M. Pelvic physiotherapy in children with functional constipation: promising but more research needed. Gastroenterology. 2017;152(8):2080–1.
24. Borowitz SM, Cox DJ, Kovatchev B, Ritterband LM, Sheen J, Sutphen J. Treatment of childhood constipation by primary care physicians: efficacy and predictors of outcome. Pediatrics. 2005;115(4):873–7.
25. Burgers R, Bonanno E, Madarena E, Graziano F, Pensabene L, Gardner W, et al. The care of constipated children in primary care in different countries. Acta Paediatr.

2012;101(6):677–80.
26. Frawley HC, Dean SG, Slade SC, Hay-Smith EJC. Is pelvic-floor muscle training a physical therapy or a behavioral therapy? A call to name and report the physical, cognitive, and behavioral elements. Phys Ther. 2017;97(4):425–37.
27. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1456–68. e2


3

Chapter 3

Physiotherapy for Children with Functional Constipation: A Pragmatic Randomized Controlled Trial in Primary Care

Jojanneke J.G.T. van Summeren, Gea A. Holtman, Boudewijn J. Kollen, Yvonne Lisman-van Leeuwen, Alice H.C. van Ulsen-Rust, Merit M. Tabbers, Janny H. Dekker, Marjolein Y. Berger

J Pediatr 2020; 216: 25-31. e2

Abstract

Objective

To determine the effectiveness of physiotherapy plus conventional treatment compared with conventional treatment alone for the treatment of functional constipation in children age 4-17 years in primary care.

Study design

Pragmatic randomized controlled trial with 8 months follow-up. Primary care physicians recruited children diagnosed with functional constipation (n = 234), and pediatricians recruited newly referred children with a diagnosis of functional constipation (n = 11). Conventional treatment comprised toilet training, nutritional advice and laxative prescribing, whereas physiotherapy focused on resolving dyssynergic defecation. The primary outcome was treatment success over 8 months, defined as the absence of functional constipation (Rome III criteria) without laxative use. Secondary outcomes included the absence of functional constipation irrespective of continuation of laxative use and global perceived treatment effect.

Results

Children were allocated to conventional treatment plus physiotherapy or conventional treatment alone (67 per group), mean (SD) age was 7.6 (3.5) years. Results of longitudinal analyses in the intention-to-treat population showed that the treatment success percentage was not statistically improved by adding physiotherapy to conventional treatment (adjusted relative risk [aRR] 0.80, 95% CI 0.44-1.30). At 4 months, fewer children receiving physiotherapy had treatment success (17%) than children receiving conventional treatment alone (28%), but this had equalized by 8 months (42% and 41%, respectively). The percentage of children without functional constipation, irrespective of continuation of laxative use, was not statistically different between groups over 8 months (aRR 1.12, 95% CI 0.82-1.34). Notably, parents reported significantly more global symptom improvement after physiotherapy than after conventional treatment (aRR 1.40; 95% CI 1.00-1.73).

Conclusions

We find no evidence to recommend physiotherapy for all children with functional constipation in primary care.

Introduction

Childhood functional constipation is a common problem worldwide.[1] It is characterized by bothersome and often embarrassing symptoms that include abdominal pain, painful bowel movements, large stools, and fecal incontinence.[2,3] Children with functional constipation are more likely than their peers to suffer low self-esteem and bullying, which negatively affect their quality of life and that of their families.[4,5,6,7] At present, the management of functional constipation tackles its multifactorial nature, with focus on toilet training, dietary advice, reassurance, and education, but it is not evidence based.[8,9] Laxatives are also recommended as a first-line treatment, but the quality of evidence on the effectiveness of laxatives is low and adherence to the advised dosage is problematic.[8,10,11,12] The lack of evidence for either of these options risks heterogeneous management and inadequate therapeutic responses.[3] Indeed, it has been reported that 50% of children with functional constipation have persistent symptoms after 6-12 months of conventional treatment and that 25% have symptoms that persist into adulthood.[13,14] Predicting which children will profit from treatment is difficult, as the evidence regarding prognostic factors is inconsistent.[8,14]

The pathophysiology underlying functional constipation is poorly understood, but it is thought that many children have dyssynergic defecation.[15,16] This refers to a dysfunction in the interaction between pelvic floor and abdominal muscles, where a failure to obtain appropriate intra-abdominal pressure during bowel movements is compounded by paradoxical contraction of the pelvic floor.[16,17,18,19] Two small randomized controlled trials (RCTs) in secondary and tertiary care have shown some positive effects when specialist physiotherapists offered pelvic floor and abdominal muscle training to resolve this dyssynergy.[20,21] Given that functional constipation is associated with increased medical costs,[22,23] physiotherapy in an early stage, when effective, could prevent relapses and reduce referrals to secondary care, thereby reducing costs.

In this pragmatic RCT, we aimed to determine the effectiveness of physiotherapy plus conventional treatment compared with conventional treatment alone over 8-month follow-up period for the treatment of functional constipation in children age 4-17 years in primary care in the Netherlands.

Methods

The design of this pragmatic RCT has been published in detail elsewhere.[24] This was approved by the Medical Ethical Board of the University Medical Center of Groningen (METC2013/331) and was registered in the Netherlands Trial Register (NTR4797). Parents of all children, and children themselves if age ≥12 years, provided written informed consent.

Children age 4-17 years diagnosed with functional constipation by their primary care physician (PCP) were considered eligible for participation. Between September 2014 and March 2017, participating PCPs (n = 209) recruited consecutive children presenting with functional constipation (incident cases PCP), and general pediatricians from 5 outpatient departments in the north of the Netherlands recruited consecutive children who were newly referred with a diagnosis of functional constipation (incident cases pediatrician). Any child who had consulted a PCP for functional constipation in the preceding 12 months also received a leaflet explaining the study, plus a short questionnaire to assess eligibility (eg, presence of functional constipation symptoms or laxative use in the preceding 4 weeks [prevalent cases PCP]). We excluded children with psychopathology who could affect protocol adherence, those with severe or terminal illness (physician determined), and those who had received physiotherapy or urotherapy for constipation within the past 3 years.

Randomization, stratification, and blinding

Eligible children were randomly allocated in a 1:1 to 1 of 2 treatment groups, using a computer-generated randomization list with random block sizes. The list was maintained by a researcher who was not involved in the study and had no access to the allocation site. Group randomization was stratified by age (4-8 years and 9-17 years). The allocation sequence was concealed from the researcher who assigned participants to the study groups. As we did a pragmatic trial, we did not blind practitioners and participants to group allocation, but we did blind practitioners to questionnaire answers, and data-analysts were blinded to group allocation during analysis.[25,26]

Interventions

Children in the control group received conventional treatment only, which involved education, dietary advice, toilet training, and laxative prescribing according to Dutch guidelines for the management of functional constipation.[27] These are comparable with international guidelines.[8] No restrictions or specific instructions were given to physicians regarding conventional treatment.

Children in the intervention group received conventional treatment plus physiotherapy that was carried out by specialist physiotherapists (ie, with a master's degree in pediatric or pelvic physiotherapy and certified after additional postgraduate training in the treatment of bladder and bowel dysfunction in children). These primary care physiotherapists are readily accessible in the Netherlands. A structured physiotherapy program was developed that had 6 defecation-related goals: (1) improving knowledge about defecation and the role of the child and/or parent in symptom persistence; (2) improving toilet behavior and posture; (3) increasing awareness of the sensation of needing to defecate; (4) learning to relax while defecating; (5) learning to generate adequate intra-abdominal pressure during defecation; and (6) teaching effective straining during defecation.[24] Programs were tailored to each patient and delivered in a manner appropriate to his or her developmental age and locomotor skills, allowing a maximum of 9 half-hour sessions. Physiotherapy was ended earlier if the physiotherapist considered that treatment was successful or that no further improvement was expected.

Outcome measurements

The primary outcome was the difference in treatment success over time between the intervention and control groups. Treatment success was defined as meeting no more than 1 of the 6 Rome III criteria, with no laxative use for 4 weeks before measurement (absence of functional constipation without laxative use).[28] Rome III criteria were assessed with the standardized Questionnaire on Pediatric Gastrointestinal Symptoms Rome III, adapted to evaluate symptoms over 4 weeks instead of 2 months, consistent with the new Rome IV criteria.[29] The questionnaire was completed by parents (for children age 4-12 years) or children themselves (if age 13-17 years). In all cases, parents answered the question "Did your child use laxatives in the past 4 weeks?" (yes or no).

The main secondary outcome was treatment success over time, as defined for the primary outcome, but irrespective of recent laxative use (absence of functional constipation, laxatives allowed). Quality of life was measured by asking parents to complete the emotional and social functioning subdomains of the defecation disorder list,[30,31] which have good internal consistency and construct validity.[31,32] Finally, the global perceived effect of treatment was evaluated with the question "To what extent are the child's symptoms changed compared with the start of the study?" that was scored on a 9-point Likert-type scale.[33] Treatment was considered effective when parents reported their child to be very much or much improved.

All outcomes were measured at baseline and at 4 and 8 months thereafter. Other baseline data included age, sex, duration of symptoms, and chronic laxative use (defined as continuous or intermittent laxative use in the 12 months before inclusion).

Statistical analyses

The sample size was estimated at 128 children based on an expected treatment success of 50% in the control group after 8 months,14 with physiotherapy hypothesized to improve success by an additional 25% (10% loss to follow-up, alpha 0.05, power 0.80).[20,24,34]

We performed multilevel analysis of our longitudinal data using MLwiN 3.01 (Center for Multilevel Modelling, University of Bristol, United Kingdom). The first and second levels were the time of measurement and the patient, respectively. An iterative generalized least squares algorithm was used to estimate the regression coefficients, and the Wald test was set to obtain P values for each coefficient. To facilitate interpretation, we converted each OR to a relative risk (RR), as follows:

RR = OR/[1 + control event rate (OR − 1)].[35]

Logistic and linear multilevel analyses were used to investigate the differences between study groups over time. Analyses were adjusted for clinically relevant baseline differences. We did not impute missing data because this is considered redundant in longitudinal datasets.[36] We based the primary analyses on an intention-to-treat population and set the significance level at a 2-sided P value of <.05. A secondary per-protocol analysis was conducted for the primary and the secondary outcomes of treatment success. The intention-to-treat population included all patients who provided informed consent and were randomly allocated to a treatment group, irrespective of whether they received that treatment. The per-protocol population comprised patients who completed the assigned interventions and assessments.[37] Propensity scores were used if imbalances occurred in the per-protocol population.[37] A preplanned subgroup analysis was performed to evaluate whether the effect of the intervention was different for children with and without chronic laxative use at baseline.

Finally, in a univariate logistic regression analyses, predictors for treatment success after 8 months were identified in the whole study population out of a preselected set of baseline clinical symptoms (P < .1).

Results

Participants

The Figure summarizes the participant flow for 134 children randomly assigned to the study groups between September 2014 and March 2017. Among all recruiting physicians, 71 GPs and pediatricians in 3 district hospitals actually included at least 1 patient to the study. Patient characteristics are shown in Table 1. Although clinically relevant differences existed

for symptom duration and chronic laxative use, we only adjusted for chronic laxative use because the variables correlated. Drop-out rates at 4 and 8 months were 16% and 24%, respectively; the baseline features of drop-outs were comparable with those of completers. In the conventional treatment group, 6 children were referred to a physiotherapist because of symptom persistence, and in the intervention group, 6 children did not receive physiotherapy (Figure 1). Participants who completed physiotherapy had an average of 5.4 (SD 2.7) sessions with a median of 98 days (IQR 63-145 days) between the first and last sessions.

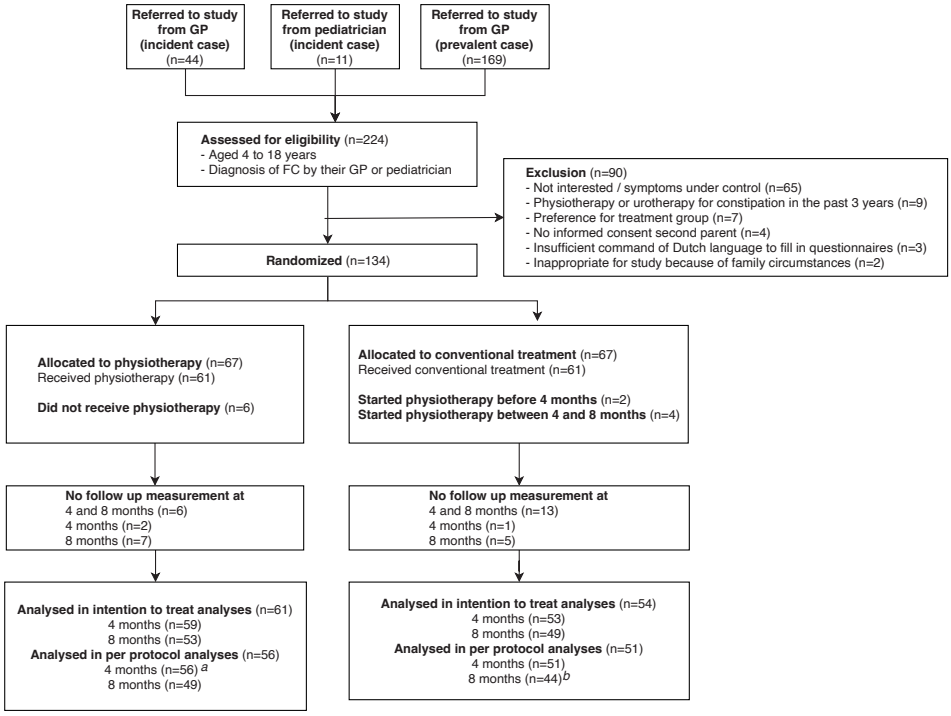


Figure 1. Flowchart of participant recruitment and participant flow through the study. Reasons for not receiving physiotherapy in the physio group were time constraints of parents/children (n = 2), symptom resolution by the time of the physiotherapy appointment (n = 1), and cancelling the appointment without a reason (n = 3). In the physiotherapy group, the number of analyzed children in the per-protocol analysis at 4 months was 56 because 3 children did not receive physiotherapy and were lost to follow-up. In the conventional treatment group, the number of analyzed children in the per-protocol analysis at 8 months follow-up was 44 because 2 children did receive physiotherapy after 4 months and were lost to follow-up at 8 months.

Table 1. Baseline characteristics (n = 134)

Characteristics	Physiotherapy (n = 67)	Conventional treatment (n = 67)
Age (y), mean +- SD	7.3 +- 3.4	7.8 +- 3.5
Girls, n (%)	38/67 (57)	44/67 (66)
Duration of symptoms, n (%)		
<3 mo	4/58 (7)	12/62 (19)
3-12 mo	6/58 (10)	10/62 (16)
> 12 mo	48/58 (83)	40/62 (65)
Chronic laxative use,*n (%)	41/57 (72)	31/58 (53)
Previous episodes of functional constipation n (%)		
>2	43/61 (71)	42/64 (66)
1	4/61 (7)	3/64 (5)
0	14/61 (21)	19/64 (30)
Use of laxatives in previous 4 wk, n (%)	46/56 (82)	44/59 (75)
Abdominal pain/discomfort 31 per wk, n (%)	35/66 (53)	41/67 (61)
Constipation-related symptoms and signs (Rome III criteria)		
<2 defecations in the toilet per wk, n (%)	16/67 (24)	10/67 (15)
Fecal incontinence 31 per wk, n (%)	26/67 (39)	34/67 (50)
Stool withholding, n (%)	22/67 (33)	18/67 (27)
Painful or hard bowel movements, n (%)	51/67 (76)	46/51 (69)
Large fecal mass in the abdomen or rectum, n (%)	36/67 (54)	38/67 (57)
Large stools that obstruct the toilet, n (%)	11/67 (16)	12/67 (18)

*Chronic laxative use was defined as continuous or regular laxative use (33 periods) in the 12 months before inclusion.

Intention-to-treat analyses

In total, 115 participants completed at least 1 of the 2 follow-up measurements and were included in the intention-to-treat analyses (Figure 1). Table 2 shows the percentage of successfully treated children after 4 and 8 months and the corresponding overall RRs. Over 8 months, success rates (absence of functional constipation and no laxative use) were not significantly different between intervention and control group (adjusted RR [aRR] 0.80, 95% CI 0.44-1.30). At 4 months, fewer children receiving physiotherapy (17%) had treatment success than children receiving conventional treatment alone (28%), but this had equalized by 8 months (42% and 41%, receptively).

When treatment success was defined as absence of functional constipation irrespective of continuation of laxatives there remained no significant differences between intervention and control group (aRR 1.12, 95% CI 0.82-1.34). However, although success rates were comparable at 4 months (68% and 64%), at 8 months the success rate was slightly higher in children receiving physiotherapy (73%) than in children receiving conventional treatment (61%). Regarding the other secondary outcomes, no longitudinal difference was found for quality of life between treatment groups (Table 2). A significant difference existed in the global perceived treatment effect between the groups, favoring the physiotherapy group (aRR 1.40, 95% CI 1.00-1.73).

Table 2. Intention-to-treat analysis of the primary and secondary outcomes after 4 and 8 months, with the aRR over 8 months

	4 months		8 months				
Outcomes	PT	CT	PT	CT	RR/b (95% CI)	aRR/b (95% CI)*	*P*
Total group, n	59	53	53	49			
Absence of functional constipation, laxatives not allowed, n (%)	10/58 (17)	14/51 (28)	22/53 (42)	20/49 (41)	0.85 (0.49–1.32)	0.80 (0.44–1.30)	.397
Absence of functional constipation, laxatives allowed, n (%)	40/59 (68)	34/53 (64)	38/52 (73)	30/49 (61)	1.12 (0.85–1.32)	1.12 (0.82–1.34)	.405
Quality of life median (IQR)	82 (75–88)	84 (74–88)	85 (79–92)	85 (77–90)	b: 0.1 (4.0 to 4.3)	b: 0.9 (5.2 to 3.4)	.675
Global perceived effect, n (%)	36/57 (63)	19/50 (38)	33/53 (62)	25/48 (52)	**1.39† (1.03–1.70)**	**1.40† (1.00–1.73)**	**.048†**

Bold values are statistically significant. b, beta coefficient.
*Adjusted for chronic laxative use.
†P < .05.
PT Physiotherapy
CT Conventional treatment

Per protocol analyses

At baseline, there were no imbalances in patient characteristics for the per-protocol population (n = 107). Analyses revealed no significant differences over time between intervention and control group when success was defined as the absence of functional constipation either without laxatives (aRR 0.88, 95% CI 0.60-1.13) or irrespective of laxative use (aRR 0.98, 95% CI 0.53-1.56).

Subgroup analyses

Table 3 shows the baseline characteristics of the subgroups of children with (n = 72) and without (n = 43) chronic laxative use. Table 4 shows the percentage of successfully treated children per subgroup after 4 and 8 months, with the corresponding RRs for the entire period. In children with chronic laxative use, we observed only a significant difference between the intervention and control group for the main secondary outcome, absence of functional constipation irrespective of continuation of laxative use (RR 1.40, 95% CI 1.00-1.63). In children without chronic laxative use, we did not observe any significant differences over time between treatment groups.

Table 3. Baseline characteristics of children with and without chronic laxative use

	Children with chronic laxative use (n = 72)*		Children without chronic laxative use (n = 43)*	
Characteristics	Physiotherapy (n = 41)	Conventional treatment (n = 31)	Physiotherapy (n = 16)	Conventional treatment (n = 27)
Age (y) mean (SD)	7.29 (3.47)	7.55 (3.82)	7.44 (3.89)	8.00 (3.21)
Girls, n (%)	25/41 (61)	25/31 (81)	8/16 (50)	14/27 (52)
Use of laxatives in previous 4 wk, n (%)	35/41 (85)	26/31 (84)	11/15 (69)	17/27 (63)
Abdominal pain/discomfort >once per wk, n (%)	19/41 (48)	17/31 (55)	10/16 (63)	18/27 (67)
Constipation-related symptoms and signs (Rome III criteria) <2 defecations in the toilet	8/41 (20)	3/31 (10)	5/16 (31)	5/27 (19)
Fecal incontinence >1 per wk, n (%)	12/41 (29)	16/31 (52)	8/16 (50)	14/27 (52)
Stool withholding, n (%)	10/41 (24)	8/31 (26)	6/16 (38)	8/27 (30)
Painful or hard bowel movements, n (%)	29/41 (71)	19/31 (61)	12/16 (75)	20/27 (74)
Large fecal mass in the abdomen or rectum, n (%)	23/41 (56)	20/31 (65)	8/16 (50)	12/27 (44)
Large stools that obstruct the toilet, n (%)	6/41 (15)	6/31 (19)	2/16 (13)	5/27 (19)

*Chronic laxative use was not known for 19 children.

Prognostic factors for treatment success after 8 months

Stool withholding, fecal incontinence, and abdominal pain were in the univariate analyses, negatively associated ($P < .1$) with treatment success of functional constipation after 8 months (Table 5).

Discussion

During the study period, we found no benefit from adding physiotherapy to conventional treatment in terms of either treatment success or quality of life. By contrast, parents in the physiotherapy group did report symptom improvement significantly more often compared with the conventional treatment group. A potential explanation for this discrepancy between outcomes is that parents of children receiving physiotherapy may have been more willing to report improvements because of the additional attention. However, it is also possible that parents valued improvements in symptoms not included in the Rome criteria. For example, abdominal pain is not considered in these criteria, but a recent study indicated that parents and children both felt that change in abdominal pain was an important treatment outcome.[38]

Comparisons with other studies

The effectiveness of physiotherapy in childhood functional constipation was previously measured in 2 studies in district (n = 53)[20] and university (n = 72)[21] hospitals. Neither study defined treatment success as the absence of functional constipation without laxative use, but one did evaluate the effectiveness of physiotherapy as the absence of functional constipation irrespective of laxative use.[20] Defined in this way, the treatment success rate

Table 4. Intention-to-treat analysis of outcomes after 4 and 8 months by chronic laxative use, with the RR over 8 months

	4 months		8 months			
	Physiotherapy	Conventional treatment	Physiotherapy	Conventional treatment	RR or b (95% CI)	P
Children with chronic laxative use	**N = 39**	**N=26**	**n = 31**	**n = 21**		
Absence of functional constipation without the use of laxatives, n (%)	8/39 (21)	6/26 (23)	15/31 (48)	8/21 (38)	1.01 (0.52–1.90)	.783
Absence of functional constipation with or without laxatives, n (%)	28/38 (74)	16/26 (62)	25/30 (83)	0/21 (48)	**1.40* (1.00–1.63)**	**.049**
Quality of life median (IQR)	82 (76–88)	87 (77–92)	87 (81–92)	88 (82–92)	b: 0.5 (4.7 to 5.7)	.850
Global perceived effect, n (%)	23/39 (59)	8/25 (32)	19/31 (61)	10/20 (50)	1.51 (0.96–1.96)	.069
Children without chronic laxative use	**N = 14**	**N=18**	**N = 15**	**N = 19**		
Absence of functional constipation without the use of laxatives, n (%)	1/14 (7)	7/18 (39)	5/15 (33)	10/19 (53)	0.46 (0.15–1.04)	.066
Absence of functional constipation irrespective laxative use, n (%)	7/14 (50)	13/18 (72)	9/15 (60)	14/19 (74)	0.77 (0.35–1.12)	.259
Quality of life median, (IQR)	78 (63–87)	83 (68–87)	80 (63–86)	82 (69–88)	b: 3.5 (11.1 to 4.2)	.374
Global perceived effect, n (%)	8/13 (62)	9/18 (50)	10/15 (67)	10/19 (53)	1.25 (0.69–1.67)	.382

*$P < .05$.

in the conventional treatment group was comparable between both studies, and similar to others,[14] but the beneficial effect of adding physiotherapy differed. We found no difference in effect between physiotherapy and conventional treatment over 8 months (OR 1.3, 95% CI 0.6-3.1), whereas a significant difference was found in the hospital study at 6 months (OR 11.7, 95% CI 1.8-78.3). Children with chronic laxative use may be overrepresented in district hospitals. In our subgroup of children with chronic laxative use, we observed a significant difference in effect between the physiotherapy and conventional treatment groups (OR 2.7, 95% CI 1.0-7.4), though to a much smaller extent than in the hospital study. The effect size in the hospital study might have been exaggerated or due to a type I error given the wide confidence interval and small sample size.[34] Other explanations for the observed differences in the added value of physiotherapy could be the heterogeneity in physiotherapy interventions and follow-up time. The outcomes measured in the university hospital study were not comparable with those used in our study.[21]

Outcomes in clinical trials of children with functional constipation have varied greatly.[39] To enhance comparison of results between studies, experts recently agreed to use treatment

success as a primary outcome in clinical trials, with success simply defined as no longer meeting Rome criteria for functional constipation.[40] Our primary outcome used a stricter definition of success that required no laxative use in the previous 4 weeks. Nevertheless, the definition used for our main secondary outcome was consistent with the expert recommendation. It was therefore unsurprising that observed treatment success rates were lower when using our strict definition. The latest guidelines also recommend using a diary to monitor functional constipation,[40] but we only used validated self-administered questionnaires to minimize the burden of the study.[28] As a consequence, information about the number of bowel movements, episodes of fecal incontinence, and daily laxative dose may be less accurate.

Strengths and weaknesses of this study

Strengths of our study include the relatively large sample size and the pragmatic design.[25,26] This design meant that practitioners and participants were not blinded and we could include the effect of the patient–caregiver relationship. In addition, the participation of a large number of practitioners who were given the flexibility to adjust treatment intensity in both interventions ensures that our results are generalizable to routine practice in the Netherlands. Despite these strengths, there are some limitations. Notably, only 60% of the eligible children were included and 24% of these did not complete all follow-up measurements. Children who refused to participate tended to be older and to have less chronic laxative use compared with participants.[24] This means that the results of this study are less generalizable to older children and to children who recently started using laxatives. To minimize the influence of drop-outs and to consider the fluctuating natural course of functional constipation, we used longitudinal analysis in the intention-to-treat population. Also, given that research has shown that 17%-41% of children relapse within the first year after treatment success, and given that 50%-60% relapse within 5 years,[41] our follow-up time of 8 months was too short to make definitive statements on the long-term preventive effect of physiotherapy on relapses. Another limitation is that we did not evaluate the effects of the different elements of the physiotherapy program. We have chosen patient relevant outcome measures, and we did not assess pelvic floor muscle (dys) synergia, as we considered this too invasive for children. Finally, our sample size was too small to perform multivariate analysis to identify prognostic factors that were independently related to treatment success after 8 months but we recommend for future research to take into account stool withholding, fecal incontinence and abdominal pain as potential prognostic factors.

Our findings mean that we must reject our hypothesis that physiotherapy is most effective in the early stages of functional constipation. However, physiotherapy in primary care might be effective for children with protracted symptoms. Children with early stages of functional

constipation and their parents are possibly insufficiently motivated to invest time in a physiotherapy treatment. This was also observed as the most important reason for children and their parents not to participate in the study.[24] Non-adherence has also been described with laxative treatment.[11] More research is needed to determine whether physiotherapy can be beneficial in primary care when started at a later stage of functional constipation, when symptoms have become more chronic and children and parents are more motivated, and whether the effect of physiotherapy can be predicted by patient factors or psychosocial circumstances related to onset.

In conclusion, we found no objective benefit from adding physiotherapy to conventional treatment for the whole group of children with functional constipation consulting in primary care, although parents were more satisfied with physiotherapy. More research is needed to evaluate whether physiotherapy in primary care is both effective and cost-effective for children with symptoms of longer duration.

Table 5. Distribution of candidate predictors in relation to 2 definitions of treatment success in the whole study population after 8 months (results of univariate logistic regression analyses)

	Model 1					Model 2				
	Absence of functional constipation and no laxatives (n = 42)	Presence of functional constipation or the use of laxatives (n = 59)	OR (95% CI)	P	R2 (Nagelkerke)	Absence of functional constipation (n = 68)	Presence of functional constipation (n = 33)	OR (95% CI)	P	R2 (Nagelkerke)
Abdominal pain, 31 wk, n (%)	19/42 (45)	37/59 (62)	0.5 (0.2-1.1)	.083	0.040	32/68 (47)	24/33 (73)	0.3 (0.1-0.8)	.017	0.082
Defecation frequency £2 wk, n (%)	0/42 (0)	6/59 (10)	0.8 (0.3-2.5)	.718	0.002	0/68 (0)	6/33 (18)	1.1 (0.3-3.4)	.895	0.000
Fecal incontinence, >1 per wk, n (%)	1/42 (2)	24/59 (41)	0.5 (0.2-1.1)	.082	0.041	4/68 (6)	21/33 (64)	0.2 (0.1-0.5)	.000	0.178
Painful or hard bowel movements, n (%)	8/42 (19)	29/59 (49)	0.9 (0.4-2.2)	.872	0.000	13/68 (19)	24/33 (73)	0.5 (0.2-1.3)	.141	0.032
Stool withholding, n (%)	0/42 (0)	15/59 (25)	0.3 (0.1-0.8)	.012	0.090	1/68 (1)	14/33 (42)	0.2 (0.1-0.4)	.000	0.207
Large stools that obstruct the toilet, n (%)	1/42 (2)	9/59 (15)	0.7 (0.2-2.2)	.565	0.004	3/68 (4)	7/33 (21)	0.9 (0.3-2.6)	.801	0.001

In model 1 treatment success is defined as absence of functional constipation according the Rome III criteria and no laxative use. In model 2 the treatment success is defined as absence of functional constipation according to the Rome III criteria irrespective of laxative use.

References

1. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr 2018;198: 121-30.
2. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterol 2011;25:3-18.
3. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem. World J Gastroenterol 2016;22:6864.
4. Kovacic K, Sood MR, Mugie S, Di Lorenzo C, Nurko S, Heinz N, et al. A multicenter study on childhood constipation and fecal incontinence: effects on quality of life. J Pediatr 2015;166:1482-7.
5. BelseyJ,GreenfieldS,CandyD,GeraintM.Systematicreview:impactof constipation on quality of life in adults and children. Aliment Pharmacol Ther 2010;31:938-49.
6. Rajindrajith S, Devanarayana NM, Weerasooriya L, Hathagoda W, Benninga MA. Quality of life and somatic symptoms in children with constipation: a school-based study. J Pediatr 2013;163:1069-72.
7. Kaugars AS, Silverman A, Kinservik M, Heinze S, Reinemann L, Sander M, et al. Families' perspectives on the effect of constipation and fecal incontinence on quality of life. J Pediatr Gastroenterol Nutr 2010;51:747-52.
8. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58:258-74.
9. Pijpers MA, Tabbers MM, Benninga MA, Berger MY. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Arch Dis Child 2009;94:117-31.
10. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database of Syst Rev, 2016:1-15.
11. Koppen IJN, van Wassenaer EA, Barendsen RW, Brand PL, Benninga MA. Adherence to polyethylene glycol treatment in children with functional constipation is associated with parental illness perceptions, satisfaction with treatment, and perceived treatment convenience. J Pediatr 2018;199:132-9.
12. Steiner SA, Torres MR, Penna FJ, Gazzinelli BF, Corradi CG, Costa AS, et al. Chronic functional constipation in children: adherence and factors associated with drug

treatment. J Pediatr Gastroenterol Nutr 2014;58:598-602.
13. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics 2010;126:e156-62.
14. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr 2010;50:256-68.
15. Rao SS, Benninga MA, Bharucha AE, Chiaarioni G, Di Lorenzo C, Whitehead WE. ANMS-ESNM position paper and consensus guidelines on biofeedback therapy for anorectal disorders. Neurogastroenterol Motility 2015;27:594-609.
16. Whitehead WE, Bharucha AE. Diagnosis and treatment of pelvic floor disorders: what's new and what to do. Gastroenterology 2010;138: 1231-5, 1235.e1-1235.e4.
17. Chase JW, Stillman BC, Gibb SM, Clarke MC, Robertson VJ, Catto-Smith AG, et al. Trunk strength and mobility changes in children with slow transit constipation. J Gastroenterol Hepatol 2009;24:1876-84.
18. van Engelenburg–van Lonkhuyzen ML, Bols EM, Benninga MA, Groen L, Chase J, de Bie R. Physiotherapy interventions for functional bladder and bowel dysfunctions in neurologically normal and otherwise healthy children. Cochrane Database of Systematic Reviews 2016.
19. Guti errez 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;35:31-8.
20. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, Verwijs WA, de Bie RA. Effectiveness of pelvic physiotherapy in children with functional constipation compared with standard medical care. Gastroenterology 2017;152:82-91.
21. Silva C, Motta M. The use of abdominal muscle training, breathing exercises and abdominal massage to treat paediatric chronic functional constipation. Colorectal Dis 2013;15:e250-5.
22. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. J Pediatr 2009;154:258-62.
23. Choung RS, Shah ND, Chitkara D, Branda ME, Van Tilburg MA, Whithead WE, et al. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. J Pediatr Gastroenterol Nutr 2011;52:47-54.
24. van Summeren JJGT, Holtman GA, Lisman-van Leeuwen Y, Louer LEAM, van Ulsen-Rust AHC, Vermeulen KM, et al. Physiotherapy plus conventional treatment versus conventional treatment only in the treatment of functional constipation in children: design of a randomized controlled trial and cost-effectiveness study in primary care. BMC Pediatr 2018;18:249.

25. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ 2015;350:h2147.
26. Ford I, Norrie J. Pragmatic trials. N Engl J Med 2016;375:454-63.
27. Nederlandse Vereniging voor Kindergeneeskunde, Nederlands Huisarts Genootschap. Richtlijn obstipatie bij kinderen van 0 tot 18 jaar; 2009. p. 1-229.
28. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527-37.
29. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2016;150:1456-68.e2.
30. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, Grootenhuis MA, Derkx BH, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. Arch Dis Child 2004;89:1124-7.
31. Bongers ME, van Dijk M, Benninga MA, Grootenhuis MA. Health related quality of life in children with constipation-associated fecal incontinence. J Pediatr 2009;154:749-53.e1.
32. Hartman EE, Pawaskar M, Williams V, McLeod L, Dubois D, Benninga MA, et al. Psychometric properties of PedsQL generic core scales for children with functional constipation in the Netherlands. J Pediatr Gastroenterol Nutr 2014;59:739-47.
33. Kamper SJ, Ostelo RW, Knol DL, Maher CG, de Vet HC, Hancock MJ. Global perceived effect scales provided reliable assessments of health transition in people with musculoskeletal disorders, but ratings are strongly influenced by current status. J Clin Epidemiol 2010;63:760-6.e1.
34. van Summeren J, Dekker J, Berger M. Pelvic physiotherapy in children with functional constipation: promising but more research needed. Gastroenterology 2017;152:2080-1.
35. Prasad K, Jaeschke R, Wyer P, Keitz S, Guyatt G. Tips for teachers of evidence-based medicine: understanding odds ratios and their relationship to risk ratios. J Gen Intern Med 2008;23:635-40.
36. Twisk J, de Boer M, de Vente W, Heymans M. Multiple imputation of missing values was not necessary before performing a longitudinal mixed-model analysis. J Clin Epidemiol 2013;66:1022-8.
37. Hern an MA, Robins JM. Per-protocol analyses of pragmatic trials. N Engl J Med 2017;377:1391-8.
38. Kuizenga-Wessel S, Steutel NF, Benninga MA, Devreker T, Scarpato E, Staiano A, et al. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. BMJ Pediatr Open 2017;1:e000017.

39. Kuizenga-Wessel S, Heckert SL, Tros W, van Etten-Jamaludin FS, Benninga MA, Tabbers MM. Reporting on outcome measures of functional constipation in children—a systematic review. J Pediatr Gastroenterol Nutr 2016;62:840-6.
40. Koppen IJN, Saps M, Lavigne JV, Nurko S, Taminiau JAJM, Di Lorenzo C, et al. Recommendations for pharmacological clinical trials in children with functional constipation: the Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterol Motil 2018;30: e13294.
41. van Ginkel R, Reitsma JB, Büller HA, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond puberty. Gastroenterology 2003;125:357-63.

Chapter 4

Cost-effectiveness of physiotherapy in childhood functional constipation: a randomized controlled trial in primary care

Jojanneke J.G.T. van Summeren, Gea A. Holtman, Yvonne Lisman-van Leeuwen, Alice H.C. van Ulsen-Rust, Karin M. Vermeulen, Merit M. Tabbers, Boudewijn J. Kollen, Janny H. Dekker, Marjolein Y. Berger

Family Practice 2022; epub ahead of print

Abstract

Objective

Health care expenditures for children with functional constipation (FC) are high, while conservative management is successful in only 50% of the children. The aim is to evaluate whether adding physiotherapy to conventional treatment (CT) is a cost-effective strategy in the management of children with FC aged 4–18 years in primary care.

Methods

A cost-effectiveness analysis was performed alongside a randomized controlled trial (RCT) with 8-month follow-up. Costs were assessed from a societal perspective, effectiveness included both the primary outcome (treatment success defined as the absence of FC and no laxative use) and the secondary outcome (absence of FC irrespective of laxative use). Uncertainty was assessed by bootstrapping and cost-effectiveness acceptability curves (CEACs) were displayed.

Results

One hundred and thirty-four children were randomized.The incremental cost-effectiveness ratio (ICER) for one additional successfully treated child in the physiotherapy group compared with the CT group was €24,060 (95% confidence interval [CI] €–16,275 to €31,390) and for the secondary outcome €1,221 (95% CI €–12,905 to €10,956). Subgroup analyses showed that for children with chronic laxative use the ICER was €2,134 (95% CI –24,975 to 17,192) and €571 (95% CI 11 to 3,566), respectively. At a value of €1,000, the CEAC showed a probability of 0.53 of cost-effectiveness for the primary outcome, and 0.90 for the secondary outcome.

Conclusions

Physiotherapy added to CT as first-line treatment for all children with FC is not cost-effective compared with CT alone. Future studies should consider the cost-effectiveness of physiotherapy added to CT in children with chronic laxative use.

Introduction

Functional constipation (FC) is a common condition among children, the prevalence ranged from 0.5% to 32.2% with a pooled prevalence of 9.5% (95% confidence interval [CI] 7.5–12.1).1 Children with FC suffer from bothersome and frustrating symptoms which negatively affect their quality of life and that of their families.[2–6] Conventional treatment (CT) includes education, dietary advice, toilet training, and prescription of laxatives.[7,8] The quality of the evidence of the efficacy of laxatives and adherence to CT is low.[9–12] Half of the children diagnosed with constipation are still struggling with this problem after 6–12-month treatment, and a quarter of the children continue to experience symptoms even into adulthood.[13,14]

The high prevalence and chronic character of constipation in children result in high health care costs.[1,15–17] In the United States, the direct yearly health care costs for children with FC were 3 times higher compared with children without FC ($3,362 vs $1,095).[15] Most costs are related to consultations (general practitioners [GPs] and paediatricians), emergency room visits, and laxatives.[15,16] These high direct health care costs remain consistent during the entire childhood.[16] In addition, FC causes higher indirect costs as children with constipation miss more school days, and parents lose workdays.[15]

Two small randomized controlled trials (RCTs) have shown positive effects of adding physiotherapy to CT in childrenn referred to a hospital setting.[18,19] Treatment early in the disease process may increase treatment success and therewith reduce health care utilization and costs. To test this hypothesis, we conducted a pragmatic RCT in primary care evaluating the effectiveness of physiotherapy added to CT compared with CT alone.[20]

Information regarding the cost-effectiveness of physiotherapy added to CT in children with FC is lacking. Therefore, we have performed a cost-effectiveness analysis (CEA) alongside the RCT. Although the RCT showed no differences between groups in treatment success for all children with FC, a CEA is valuable because differences in costs might exist between treatment groups. The aim of this study is to evaluate the cost-effectiveness of physiotherapy plus CT compared with CT alone for children with FC aged 4–18 years presenting in primary care. In addition, we evaluated the cost-effectiveness of physiotherapy for the subgroup of children with chronic laxative use.

Methods

Cost-effectiveness overview

The balance between costs and effects in the physiotherapy plus CT group was evaluated in comparison to the CT only group in a CEAs, and presented in cost-effectiveness planes (CE planes) and cost-effectiveness acceptability curves (CEACs). The CEA was conducted from a societal perspective, indicating that all costs and consequences of the competing interventions are taken into account regardless of who pays for or benefits from them.[21] We performed the CEAs evaluating two definitions of treatment success. Since the time horizon of this study was shorter than 1 year, costs and effects were not discounted.

The design of the RCT and the results of the clinical effectiveness analysis have been published elsewhere.[20,22] The trial was approved by the Medical Ethical Board of the University Medical Center of Groningen (METC2013/331) and was registered in the Netherlands Trial Register (NTR4797). We obtained written informed consent from both parent(s). In addition, children aged ≥12 years also gave informed consent themselves.

Design of the pragmatic RCT

Setting, participants, and randomization

Children were recruited in primary care and paediatric outpatient departments in the Netherlands between 10 September 2014 and 1 March 2017 and last follow-up data were received on 30 November 2017. Inclusion criteria were: age 4–18 years, and a diagnosis of FC by the GP.

Children were randomly allocated in a 1:1 ratio to the two treatment groups. Randomization was stratified according to age (4–8 and 9–18 years). Given the design of the study, we could not blind children, parents, physicians, and physiotherapists to group allocation, but physicians and physiotherapists were blinded to the questionnaire answers.[23]

Interventions

CT only

Children in the control group received CT, which was not restricted with respect to content and number of consultations and dosage of laxatives. GPs and paediatricians were instructed to adhere to the Dutch clinical guidelines for FC in children.[7,8]

Physiotherapy plus CT

Children in the intervention group received CT plus physiotherapy. The physiotherapy

consisted of a maximum of nine half-hour sessions carried out by specialist physiotherapists.[20,22]

Table 1. Baseline characteristics of children (n = 134) with FC in primary care (2014–2017).

	CT (n = 67)	Physiotherapy plus CT (n = 67)
Age (in years), mean (SD)	7.8 (3.5)	7.3 (3.4)
Girls (n, %)	44/67 (66%)	38/67 (57%)
Chronic laxative usea (n, %)	31/58 (53%)	41/57 (72%)
Previous episodes of FC (n, %)		
≥2	42/64 (66%)	43/61 (71%)
1	3/64 (5%)	4/61 (7%)
0	19/64 (30%)	14/61 (21%)
Use of laxatives in previous 4 weeks (n, %)	44/59 (75%)	46/56 (82%)
Abdominal pain/discomfort ≥ once a week (n, %)	41/67 (61%)	35/66 (53%)
Constipation related symptoms and signs (Rome III criteria)		
≤2 defecations in the toilet per week (n, %)	10/67 (15%)	16/67 (24%)
Faecal incontinence ≥1 per week(n, %)	34/67 (50%)	26/67 (39%)
Stool withholding (n, %)	18/67 (27%)	22/67 (33%)
Painful or hard bowel movements (n, %)	46/67 (69%)	51/67 (76%)
Large faecal mass in the abdomen or rectum (n, %)	38/67 (57%)	36/67 (54%)
Large stools that obstruct the toilet (n, %)	12/67 (18%)	11/67 (16%)

[a]Chronic laxative use was defined as continuous or regular laxative use (≥3 periods) in the 12 months before inclusion.

Health outcomes

The primary outcome was treatment success defined as "the absence of FC according to the Rome III criteria and no laxative use in the four weeks prior to measurement." The secondary outcome was "absence of FC irrespective of laxative use." "Absence of FC" was measured with the Questionnaire on Pediatric Gastrointestinal Symptoms Rome-III (QPGS-Rome III).[24] We modified the questionnaire to evaluate symptoms over a 4-week period instead of a 2-month period.

Costs analysis

A societal perspective incorporates direct health care costs, direct nonhealth care costs, and indirect costs due to FC. Data on costs were collected with two questionnaires, and completed by parents at baseline and after 4- and 8-month follow-up. Direct health care and direct nonhealth care costs related to FC were collected with an adapted version of the Institute of Medical Technology Assessment Medical Consumption Questionnaire (iMTA-MCQ) and indirect costs related to FC with an adapted version of the Productivity Costs Questionnaire (iMTA-PCQ).[25,26] Only questions related to potential differences in costs between the two interventions were included. In the physiotherapy group, the number of consultations to the physiotherapist was recorded by the physiotherapist.

Relevant direct health care costs that were taken into account were costs for consultations

and hospitalizations related to FC and medication prescriptions (such as laxatives). Patient and family costs (direct nonhealth care costs) were costs for faecal incontinence materials (such as diapers or mattress protectors), diet supplements, and alternative drugs and treatments. Indirect costs were costs related to work absenteeism of parents. All costs are presented in euros (€) at the price level of 2017, and calculated according to the Dutch cost manual.[27] Table 2 presents a detailed overview of the cost components included and the cost prices used. In principle, we adhered to the national guidelines for cost-effectiveness studies

Table 2. Mean costs (95% CI) and mean differences in costs between physiotherapy plus CT group and CT group alone during the 8-month follow-up period (complete cases n = 100).

Types of costs	Unit price 2017 (€)	Source	Mean costs CT (95% CI) n = 48	Mean costs physio plus CT (95% CI) n = 52	Mean difference (95% CI)
Health care costs					
GP	33.76 per consultation	CQ	27 (12 to 47)	9 (4 to 14)	−16 (−39 to −2)
Paediatrician	103.34 per consultation	CQ	19 (6 to 38)	38 (17 to 62)	19 (−10 to 46)
Physiotherapist	33.76 per consultation	RP/CQ[c]	4 (1 to 9)	206 (180 to 227)	201 (175 to 223)
Other health care professional	Variable[a]	CQ	43 (8 to 95)	33 (11 to 61)	−9 (−67 to 35)
Laxatives	Variable[b]	CQ	37 (21 to 57)	42 (16 to 68)	5 (−31 to 54)
Other health care costs (e.g. pain medication, hospitalization)	Variable	CQ	1 (0 to 2)	0 (—)	−1 (−2 to 0)
Subtotal health care costs			131 (75 to 204)	328 (256 to 412)	196 (92 to 301)
Patient and family costs					
Non-health care costs (diapers, underpants, mattress protector)	Patient reported costs	CQ	23 (5 to 49)	22 (3 to 49)	−1 (−33 to 32)
Additional diet supplements	Patient reported costs	CQ	12 (1 to 32)	7 (0 to 17)	5 (−28 to 32)
Alternative medicine cost	Patient reported costs	CQ	5 (0 to 12)	1 (0 to 1)	4 (−12 to 0)
Alternative treatment costs	Patient reported costs	CQ	1 (0 to 3)	0 (—)	−1 (−3 to 0)
Subtotal patient and family costs			41 (12 to 80)	30 (7 to 59)	−11 (−57 to 30)
Indirect costs					
Work absenteeism parents	35.55 per h	CQ	53 (0 to 139)	22 (0 to 59)	−31 (−122 to 38)
Subtotal indirect costs			53 (0 to 139)	22 (0 to 59)	−31 (−122 to 38)
Total costs all sectors			226 (111 to 368)	380 (289 to 480)	155 (−12 to 310)

CQ, cost questionnaire; h, hour; RP, registration physiotherapist. The unit price is based on the Dutch cost manual.

[a]Other health care professionals costs: out of hours service GP (€110.50 per consultation), other medical specialist (€93.11 per consultation), emergency department (€264.99 per consultation), and psychologist (€65.48 per consultation).

[b]Prices are shown per gram: Forlax (€0.05), ForlaxJR (€0.06), Movicolon (€0.01), Macrogol (€0.05), Psyllium fibres (€0.08), magnesium oxide (€0.0022 per µg), lactulose (€0.004 per mL), and sodium picosulfate (€0.25 per defined daily dose).

[c]In the intervention group, we used the number of consultations reported by the physiotherapist on the registration form, in the control group we used the number of consultations reported by parents in the cost questionnaire because those children were not referred to physiotherapy by a member of the research team, and therefore physiotherapists were not instructed to use the RP form.

of the Care Institute Netherlands for the pricing of all items including productivity costs.[21] To test the robustness of the cost outcomes, we performed univariate and multivariate sensitivity analyses in which we increased or decreased the cost prices of the three main cost items with 20%.

Cost-effectiveness analysis

An incremental CEA was undertaken to compare CT only vs physiotherapy plus CT over an 8-month time horizon. Only patients with a complete follow-up, i.e. a measurement at 4 and 8 months, were included in the CEA. If a child or parent had completed both cost questionnaire, but a specific cost item was missing, this cost was imputed at item level by imputing the mean of that item in the allocated group. In seven patients, costs at 4-month follow-up were measured over a 3-month period instead of a 4-month period. In these patients, costs were extrapolated to be representative for a 4-month period.

An incremental cost-effectiveness ratio (ICER) represents the additional costs that one intervention imposes over another, compared with the additional effects it delivers.[21] We calculated ICERs by dividing the difference in costs between the intervention and control group by the difference in effectiveness between both treatment groups. The ICER can be interpreted as the additional costs needed to treat one extra patient successfully. To calculate this, for each of the bootstrapped trial sets, means of costs and outcomes were multiplied by 100. To explore the uncertainty in the CEA, we employed a nonparametric bootstrapping technique with 5,000 replications to estimate CIs. Results of the bootstraps are presented in CE planes and CEACs. A CEAC is based on the uncertainty in cost and effect differences and shows the probability that the alternative (new) intervention is cost-effective over a range of possible values (thresholds), that a decision maker might be willing to pay for one additional unit of effect.

A predefined subgroup analysis was performed to evaluate the cost-effectiveness of the intervention for children with chronic laxative use. We defined chronic laxative use as continuous or regular laxative use (≥3 periods) in the 12 months before enrolment.
Data were analysed using SPSS Version 25.0 (IBM Corp., Armonk, NY). For bootstrapping we used Microsoft Excel 2010.

Results

In total, 134 children were included in the RCT, of which 100 children (75%) were included in the complete case analyses (Supplementary Figure 1). Baseline characteristics of children in the intervention and control group were comparable (Table 1). In addition, children lost

to follow-up (n = 32) and completers (n = 100) were comparable with respect to baseline characteristics and baseline health care costs.

Table 2 presents the mean costs per child during the 8-month follow-up period. Mean costs per child were €380 (95% CI €289– 480) in the physiotherapy plus CT group and €226 (95% CI €111– 368) in the CT only group. The mean costs for the physiotherapy intervention were €206 (95% CI 180–227) per child. Without taking these physiotherapy intervention costs into account, total costs were slightly lower in the intervention group (€174) compared with the CT group (€226), differences in costs per sector were: health care costs (€122 vs €131), patient and family costs (€30 vs €41), and indirect costs (€22 vs €53) per child.

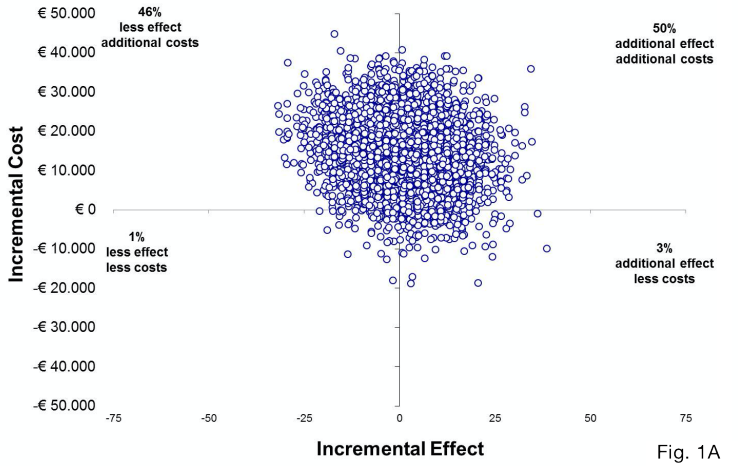
In the main analysis, the total costs were €155 higher in the intervention group compared with the control group. The results of the univariate and multivariate sensitivity analyses did not have a large impact on this difference in total costs between groups. The differences in costs ranged between €113 and €195 in the multivariate analyses.

After 8 months, the percentages of successfully treated children according to the primary outcome (no FC and no laxatives), and according to the secondary outcome (no FC irrespective of laxative use) were 42% and 75% in the physiotherapy plus CT group and 42% and 63% in the CT group, respectively (Table 3).

The CEA showed an ICER of €24,060 (95% CI −16,275 to 31,390). This means, the incremental cost of treating one additional child successfully with physiotherapy plus CT compared with CT alone is €24,060 (95% CI €−16,275 to €31,390) (Table 3). Fifty percent of the bootstrap simulations were in the north-east quadrant, indicating that they represented a better outcome and higher costs, and 46% were in the north-west quadrant, representing a worse outcome and higher costs (Figure 1a). The CEA curve (Supplementary Figure 2a) shows for a number of potential willingness to pay values the probability that physiotherapy plus CT is cost-effective; the maximum probability was 0.53. Results of the sensitivity analyses were unlikely to change the conclusions.

Table 3 and Figure 1b show that the ICER to gain one additional patient without FC irrespective of the use of laxatives was €1,221 (95% CI −12,905 to 10,956). The CEA curve (Supplementary Figure 2b) shows a maximum probability of physiotherapy plus CT being cost-effective of 0.90. If society is willing to pay an extra €500 or €1,000 the probability that physiotherapy plus CT is cost-effective compared with CT is, respectively, 0.47 and 0.90.

In Supplementary Table 1, the costs and effects and the results of the CEAs in the subgroup of children with chronic laxative use are shown. The difference in treatment success percentages was for the primary and secondary outcome, respectively, 10% (95% CI −17%



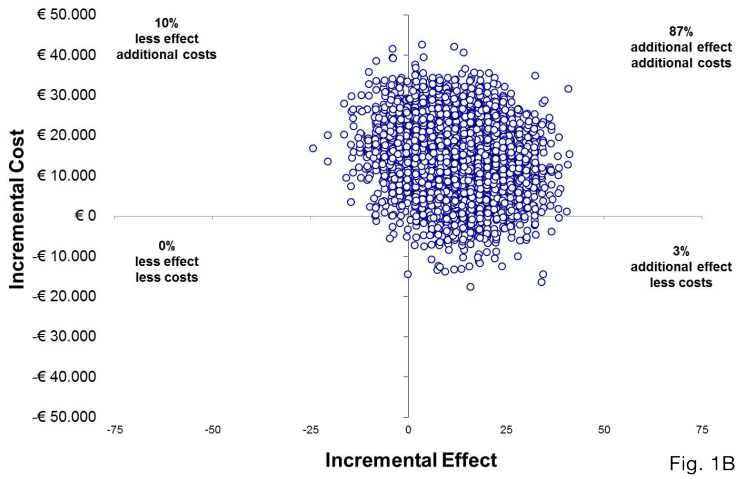


Figure 1. Incremental cost-effectiveness (CE) planes for the total sample (n = 100): 5,000 bootstrap replications for the mean difference between costs and effects. In the cost-effectiveness planes, the differences in costs were shown on the horizontal axis and differences in treatment effects on the vertical axes. In (a) treatment success is defined as no FC and no laxative use; and in (b) as no FC irrespective of continued laxative use. In order to show the costs per additional successfully treated child costs and treatment success rates were multiplied by 100. As an example, bootstrapped cost-effectiveness pairs located in the north-east quadrant showed physiotherapy plus CT to be more effective, but more costly than CT alone, and bootstrapped cost-effectiveness pairs located in the north-west quadrant showed physiotherapy plus CT is less effective and more costly than CT alone.

Table 3. Results of cost-effectiveness analyses based on complete case analyses (n = 100).

	Effects			ICER	Alternative 95% CI	Distribution (%) cost-effectiveness plane quadrants			
	CT (n = 48)	Physio plus CT (n = 52)	Mean differences (alternative 95% CI)		2.5–97.5	North east ☹☺	North west ☹☹	South west ☺☹	South east ☺☺
Absence of FC and no laxatives (n, %)	20 (42)	22 (42)	0.64 (−0.17 to 0.22)	24,060a	−16,275 to 31,390	50	46	1	3
Absence of FC (n, %)	30 (63)	38 (75)	12.01 (11.76 to 12.26)	1,221a	−12,905 to 10,956	85	11	0	4

[a]ICERs are displayed in additional costs to treat one extra person successful. The blue smiley is related to the costs and the green one to the effects of physiotherapy plus CT compared with CT alone. Thus, the north-east quadrant means physiotherapy plus CT is more effective, but more costly than CT alone, the north-west quadrant physiotherapy plus CT is less effective and more costly than CT alone, the south west quadrant physiotherapy plus CT is less effective, but less costly than CT alone, the south east quadrant physiotherapy plus CT is more effective and less costly than CT alone.

to 37%) and 36% (95% CI 11% – 61%) in favour of the physiotherapy plus CT group. Societal costs related to FC were for the CT group €139 (51–274) and for the physiotherapy plus CT group €364 (95% CI 249–505) in 8 months.

Most of the bootstrap replications for the primary outcome (76%), and almost all replications for the secondary outcome (98%) were in the north-east quadrant, indicating more effects but at higher costs, resulting in an ICER of €2,134 and €571, respectively. The maximum probability physiotherapy added to CT is cost-effective compared with CT alone in children with chronic laxative use was 0.77 according to the primary outcome, and 0.98 according to the secondary outcome. If society is willing to pay an extra €500 or €1,000 euro the probability that physiotherapy plus CT is cost-effective compared with CT alone according to the primary outcome is, respectively, 0.12 and 0.24 and according to the secondary outcome 0.45 and 0.81.

Discussion

Adding physiotherapy to CT in the treatment of all children with FC in primary care is not considered cost-effective compared with CT alone according to the primary outcome. Currently, in the Netherlands there is no explicit cost-effectiveness threshold for our primary as well as our secondary outcome. Therefore, a firm conclusion regarding cost-effectiveness of physiotherapy plus CT cannot be drawn. However, regardless of the maximum amount of money society would be willing to pay, the probability that physiotherapy added to CT will be cost-effective compared with CT alone according to the primary outcome will not exceed 0.5. In case treatment success is defined according to the secondary outcome, the maximum probability that physiotherapy added to CT will be successful is 0.90. If society is willing to pay an incremental cost of €500 or €1,000 the probability that physiotherapy added to CT

is cost-effective compared with CT alone is, respectively, 0.47 and 0.90. The ICER showed that the cost-effectiveness of physiotherapy added to CT seems to be larger for children with chronic laxative use. However, this was less obvious in the CEAC analyses, which are based on the uncertainty in cost and effect differences. Further evaluation in children with chronic laxative use is needed.

In the literature treatment, success is recommended as primary outcome in studies investigating childhood FC, however, there is no agreement on the definition of treatment success.[28,29] A strength of this study is that we have used two frequently used definitions of treatment success: "the absence of FC and no laxatives," and "the absence FC irrespective of laxative use." The definition of treatment success affected the results and conclusions of our CEAs. In future meta-analyses, this impact of the definition of treatment success on the results of (cost)-effectiveness analyses needs to be taken into consideration.

To our knowledge this is the first study that evaluated the cost-effectiveness of an intervention in children with FC. Therefore, there is no way to set the cost-effectiveness of the physiotherapy intervention against cost-effectiveness of other interventions for the management of childhood FC. In agreement with the literature this study showed that—setting aside costs for physiotherapy—consultations to the GP, paediatrician, and costs for laxatives were the most prominent direct health care costs.[15,16] In our study, we only took into account those costs that were potentially different between interventions, and therefore, fixed health care costs, such as registration costs in general practice, were not taken into account. Furthermore, although we measured indirect costs due to school absenteeism of the child, such as hiring a babysitter, these costs were not included in our analyses as there is no clear policy for the inclusion of these kind of costs. In this study, these costs were negligible.

This study was powered on clinical outcomes and not on cost-effectiveness. However, this is almost never the case in cost-effectiveness studies performed alongside clinical trials because many more participants are needed for a sufficient power of 80% due to the skewed nature of costs. From an ethical point of view this would not be acceptable. To include more information regarding uncertainty, we applied bootstrapping and present uncertainty in the cost-effectiveness planes using alternative 95% CIs. Uncertainty is also represented in the CEACs and the outcomes of the sensitivity analyses.

The current time horizon was limited to the duration of the follow-up of the trial. One of the advantages of this approach is that it enables collection of both costs and clinical outcomes in detail and on a patient level. Short-term outcomes are therefore rather precise. As

participation in studies is time consuming for participants, long-term estimations usually have to rely on assumptions and modelling approaches.

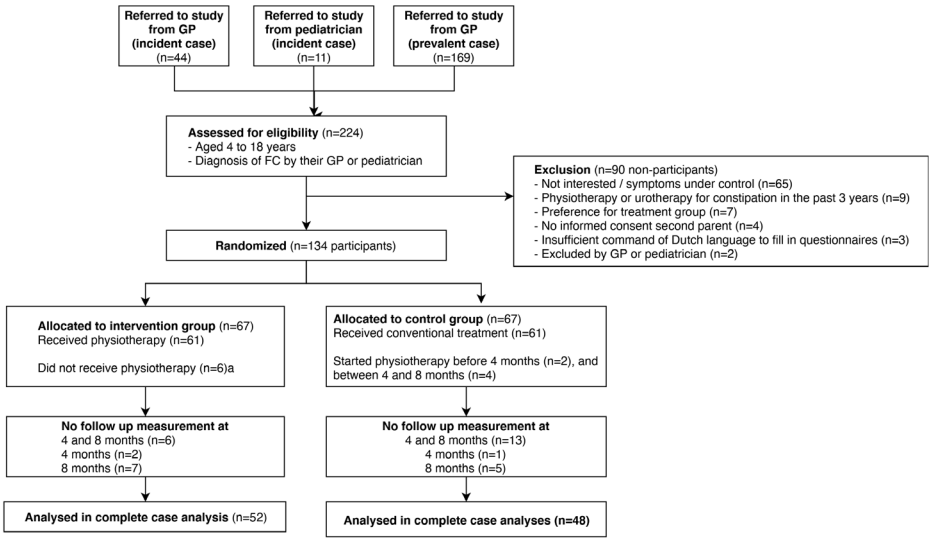
Data regarding health care consumption and productivity were collected using a self-assessed questionnaire. This might induce a self-report bias, however, we think the precision in the cost estimation outweighs this bias, as compared with only using officially registered data. Moreover, since we depend on incremental costs, this bias would be comparable between groups.

We have not presented the results of the cost–utility analysis because the analysis showed that the adult tariffs were not reliable as a proxy for the child tariffs. In fact, the cost–utility analysis showed that a substantial part of the utility scores based on the adult tariffs were below zero, indicating a very low QoL, while parents reported on another QoL question with a scale of 0–100 a mean health status of 85 for their child.

In this study we defined children with chronic laxative use as children with continuous or regular laxative use (≥3 periods) for over 12 months. We did not measure the exact period a child had symptoms and used laxatives. More research is needed to investigate whether duration of symptoms is related to the effects of physiotherapy, and whether there might be an optimal timing for starting physiotherapy. This is of relevance for the CEA in the subgroup population.

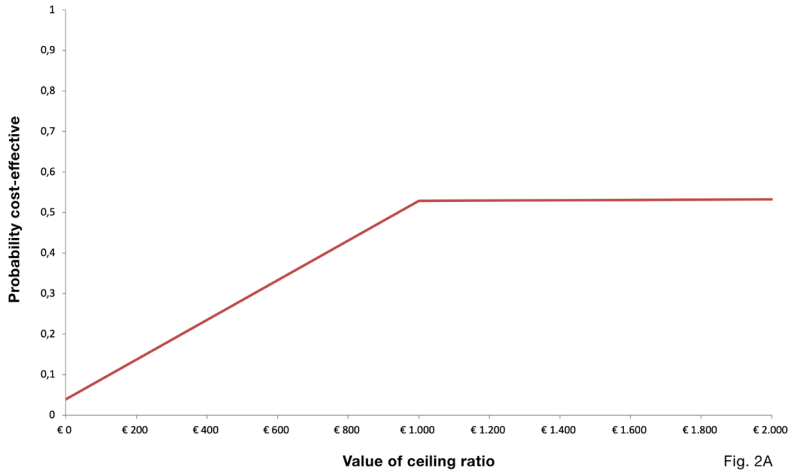
Previous studies showed that health care costs for children with FC are higher than for children without FC during their entire childhood and that children (and their parents) do often search for alternative therapies when a child does not respond to laxatives.[16,30] The time horizon of this study was limited to 8 months, which is too short to evaluate whether physiotherapy has an effect on the number of relapses or recurrences, which might influence long-term costs. Future research has to evaluate whether physiotherapy might reduce long-term health care costs.

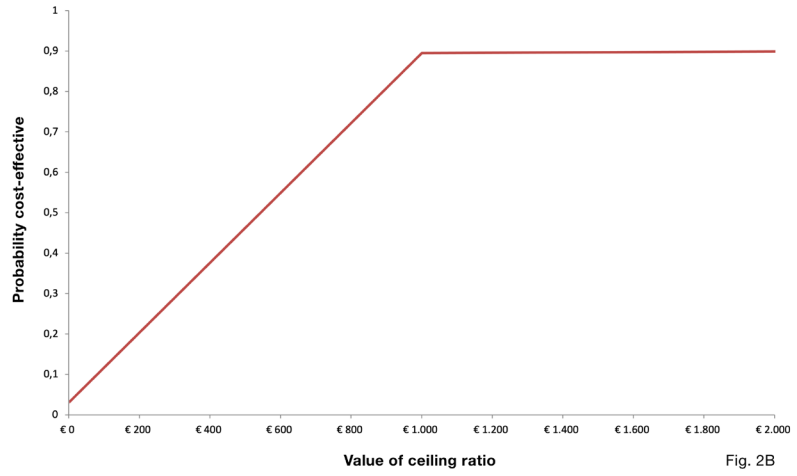
In conclusion, physiotherapy treatment for all children with FC in primary care is not considered cost-effective. For children with chronic laxative use, the cost-effectiveness of physiotherapy needs further evaluation.



Supplemental Figure 1. Flowchart of participant flow Abbreviations: FC, Functional constipation, GP, General practitioner
a Reasons for not receiving physiotherapy were: time constraints of parents/children (n=2), free of symptoms at time of physiotherapy appointment (n=1), did not show on appointment without a reason (n=3).

Supplementary Figure 1. Flowchart of participant flow. FC, functional constipation; GP, general practitioner. aReasons for not receiving physiotherapy were: time constraints of parents/children (n = 2), free of symptoms at time of physiotherapy appointment (n = 1), not showing up at the appointment without a reason (n = 3).laxative use.





Supplementary Figure 2. The cost-effectiveness acceptability curves (CEACs) showed the probability that physiotherapy added to conventional treatment (CT) is cost effective in comparison to CT only over a range of willingness to pay thresholds. In (a) treatment success is defined as no functional constipation and no laxative use; and in (b) as no functional constipation irrespective of continued

References

1. Koppen IJN, Vriesman MH, Saps M, Rajindrajith S, Shi X, van Etten-Jamaludin FS, Di Lorenzo C, Benninga MA, Tabbers MM. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr. 2018;198:121–130.e6. doi:10.1016/j. jpeds.2018.02.029.
2. Kuizenga-Wessel S, Steutel NF, Benninga MA, Devreker T, Scarpato E, Staiano A, Szajewska H, Vandenplas Y, Tabbers MM. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. BMJ Paediatr Open. 2017;1(1):e000017. doi:10.1136/ bmjpo-2017-000017.
3. Belsey J, Greenfield S, Candy D, Geraint M. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31(9):938–949.
4. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2016;150(6):1456–1468.e2.
5. Kaugars AS, Silverman A, Kinservik M, Heinze S, Reinemann L, Sander M, Schneider B, Sood M. Families' perspectives on the effect of constipation and fecal incontinence on quality of life. J Pediatr Gastroenterol Nutr. 2010;51(6):747–752.
6. Varni JW, Bendo CB, Nurko S, Shulman RJ, Self MM, Franciosi JP, Saps M, Pohl JF; Pediatric Quality of Life Inventory (PedsQL) Gastrointestinal Symptoms Module Testing Study Consortium. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. J Pediatr. 2015;166(1):85–90.e2.
7. Nederlandse Vereniging voor Kindergeneeskunde, Nederlands Huisarts Genootschap. Richtlijn obstipatie bij kinderen van 0 tot 18 jaar [Internet]. 2021. https://richtlijnendatabase.nl/richtlijn/obstipatie_bij_kinderen_van_0_tot_18_jaar/obstipatie_-_startpagina.html.
8. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, Staiano A, Vandenplas Y, Benninga MA; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; North American Society for Pediatric Gastroenterology. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58(2):258–274.
9. Gordon M, MacDonald JK, Parker CE, Akobeng AK, Thomas AG. Osmotic and stimulant laxatives for the management of childhood constipation. Cochrane Database Syst Rev. 2016;2016(8):CD009118.
10. Pijpers MA, Tabbers MM, Benninga MA, Berger MY. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature

review on the effect of laxative treatment and dietary measures. Arch Dis Child. 2009;94(2):117–131.
11. Koppen IJ, van Wassenaer EA, Barendsen RW, Brand PL, Benninga MA. Adherence to polyethylene glycol treatment in children with functional constipation is associated with parental illness perceptions, satisfaction with treatment, and perceived treatment convenience. J Pediatr. 2018;199:132–139.
12. Steiner SA, Torres MR, Penna FJ, Gazzinelli BF, Corradi CG, Costa AS, Ribeiro IG, de Andrade EG, do Carmo Barros de Melo M. Chronic functional constipation in children: adherence and factors associated with drug treatment. J Pediatr Gastroenterol Nutr. 2014;58(5):598–602.
13. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics. 2010;126(1):e156–e162.
14. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. J Pediatr Gastroenterol Nutr. 2010;50(3):256–268.
15. Liem O, Harman J, Benninga M, Kelleher K, Mousa H, Di Lorenzo C. Health utilization and cost impact of childhood constipation in the United States. J Pediatr. 2009;154(2):258–262.
16. Choung RS, Shah ND, Chitkara D, Branda ME, Van Tilburg MA, Whitehead WE, Katusic SK, Locke GR 3rd, Talley NJ. Direct medical costs of constipation from childhood to early adulthood: a population-based birth cohort study. J Pediatr Gastroenterol Nutr. 2011;52(1):47–54.
17. Ansari H, Ansari Z, Lim T, Hutson JM, Southwell BR. Factors relating to hospitalisation and economic burden of paediatric constipation in the state of Victoria, Australia, 2002–2009. J Paediatr Child Health. 2014;50(12):993–999.
18. Silva CA, Motta ME. The use of abdominal muscle training, breathing exercises and abdominal massage to treat paediatric chronic functional constipation. Colorectal Dis. 2013;15(5):e250–e255.
19. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, Verwijs WA, de Bie RA. Effectiveness of pelvic physiotherapy in children with functional constipation compared with standard medical care. Gastroenterology. 2017;152(1):82–91.
20. van Summeren JJGT, Holtman GA, Lisman-van Leeuwen Y, Louer LEAM, van Ulsen-Rust AHC, Vermeulen KM, Kollen BJ, Dekker JH, Berger MY. Physiotherapy plus conventional treatment versus conventional treatment only in the treatment of functional constipation in children: design of a randomized controlled trial and cost-effectiveness study in primary care. BMC Pediatr. 2018;18(1):249.
21. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. New York, Oxford: Oxford University

Press; 2015.
22. van Summeren JJGT, Holtman GA, Kollen BJ, Lisman-van Leeuwen Y, van Ulsen-Rust AHC, Tabbers MM, Dekker JH, Berger MY. Physiotherapy for children with functional constipation: a pragmatic randomized controlled trial in primary care. J Pediatr. 2020;216:25–31.e2.
23. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. BMJ. 2015;350:h2147.
24. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, Walker LS. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527–1537.
25. Bouwmans C, Hakkaart-van Roijen L, Koopmanschap M, Krol M, Severens H, Brouwer W. Handleiding iMTA productivity cost questionnaire (iPCQ). Rotterdam, The Netherlands: iMTA, Erasmus Universiteit. 2013.
26. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van Roijen L. iMTA medical consumption questionnaire: Handleiding. Rotterdam, the Netherlands: Institute for Medical Technology Assessment, Erasmus Universiteit Rotterdam; 2013.
27. Hakkaart-van Roijen L, Van der Linden N, Bouwmans C, Kanters T, Tan SS. Kostenhandleiding. Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. In opdracht van Zorginstituut Nederland Geactualiseerde versie. 2021. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/ publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn+voor+het+uitvoeren+van+economische+evaluaties+in+de+gezondheidszorg+(verdiepingsmodules).pdf.
28. Kuizenga-Wessel S, Heckert SL, Tros W, van Etten-Jamaludin FS, Benninga MA, Tabbers MM. Reporting on outcome measures of functional constipation in children—a systematic review. J Pediatr Gastroenterol Nutr. 2016;62(6):840–846.
29. Koppen IJ, Saps M, Lavigne JV, Nurko S, Taminiau JA, Di Lorenzo C, Benninga MA. Recommendations for pharmacological clinical trials in children with functional constipation: the Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterol Motil. 2018;30(4):e13294.
30. van Mill M, Koppen I, Benninga M. Controversies in the management of functional constipation in children. Curr Gastroenterol Rep. 2019;21(6):23.

Chapter 5

Parent-child Agreement on Health-Related Quality of Life in Children With Functional Constipation in Primary Care

Jojanneke J.G.T. van Summeren, Jan Willem Klunder, Gea A. Holtman, Boudewijn J. Kollen, Marjolein Y. Berger, and Janny H. Dekker

J Pediatr Gastroenterol Nutr 2018; 67: 726-731

Abstract

Objective

Functional constipation (FC) has a major impact on the health related quality of life (HRQoL) of children. The aim of this study was to evaluate parent-child agreement on HRQoL in children (8 to 17 years) with FC in primary care.

Methods

Children diagnosed with FC by their clinician were eligible. HRQoL was measured with the Defecation Disorder List (DDL, score 0-100), and the EuroQol™-5-Dimension-Youth Visual Analogue Scale (EQ-5D-Y-VAS, scale 0-100). Parent-child agreement was examined with discrepancy scores, Intraclass Correlation Coefficients (ICC) and Bland-Altman plots.

Results

Fifty-six children, median age of 10 years (IQR 8-12) and their parents were included. Parent-child agreement at a group level was good, with an ICC of 0.80 (95%-CI 0.67-0.88) for the DDL, and 0.78 (95%-CI 0.65-0.87) for the EQ-5D-Y-VAS. Mean discrepancy scores for the DDL and EQ-5D-Y-VAS were small: -2.6 and -2.9, implying that parents were slightly more positive about the HRQoL than their children. Bland-Altman plots showed considerable discordance between individual parent-child pairs. Limits of agreement were -19.7 and 14.6 for the DDL and -27.6 and 21.8 for the EQ-5D-Y-VAS.

Conclusion

There is good parent-child agreement on HRQoL in children with FC at group level. However, a substantial number of parent-child pairs differed considerably on their rating of the HRQoL of the child. Therefore, we recommend clinicians, if they want to have an impression of the impact of the FC on the HRQoL of the child, to ask both the child and the parent(s).

Introduction

Functional constipation (FC) is a common disorder in children, with a pooled prevalence rate of 9.5 percent.[1] FC has a major impact on the health related quality of life (HRQoL) of children and their families, with the greatest influence on the emotional and social aspects of life.[2-5] Parental emotional perceptions of illness are correlated to treatment adherence in children with FC.[6] Therefore, it is important for clinicians to ask for the consequences of the FC for the wellbeing of the child.[7] In research, HRQoL is identified by experts as an important outcome measure in clinical trials evaluating new interventions for childhood FC.[7, 8]

There is substantial debate in the health outcomes literature regarding the most appropriate respondent for assessing children's HRQoL: the child self or the parent(s).[9-13] As HRQoL pertains to an individual's subjective perceptions, a child's self-report would represent the child's situation best.[10, 12] A parent might provide more valid information concerning more abstract health related concepts, i.e. the emotional impact of illness.[10] However, a potential drawback of a parent's report might be that it is affected by the impact of the child's condition on the family life.[10, 14] Therefore, information about the agreement between child and parent perceptions of HRQoL of the child is important in order to answer the question whether child self-reports and a parent proxy-reports are interchangeable.

In young children, a parent-proxy report will be the only option to assess HRQoL.[10, 15] In children from the age of 8 years clinicians and researchers can rely on a parent proxy-report and a child self-report when they need to be informed on the HRQoL.[15, 16] However, for practical reasons one often relies on one of the two reports. Previous studies investigating the agreement between child and parents perceptions of HRQoL reported inconsistent results.[10, 13, 17, 18] In general, it seems that parents were more negative than their child on the HRQoL if their child had a chronic disease, and more positive if the child was healthy.[10, 13, 17-19] In addition, parent-child agreement might be influenced by age and gender of the child, but the relationship between the child's age and gender and parent-child agreement is uncertain.[17]

Only one previous study has examined parent-child agreement in children with FC. This was a population from a university hospital.[20] The level of agreement in that study was low, and therefore, the authors advised to use both a parent proxy and a child self-report to measure HRQoL. In the Netherlands, children with FC are first seen in primary care. Children with diagnostic or therapeutic problems will be referred to the pediatrician or pediatric gastroenterologist. Therefore, the selection of patients with FC seen in primary

care is different from that seen in a university hospital. This difference in case-mix might influence parent-child agreement. Therefore we designed a study to examine parent-child agreement on HRQoL in children (aged 8–17 years) with FC in primary care. Secondary aim was to investigate whether agreement was associated with age or gender of the child.

Methods

Study design and participants

This study was designed as an agreement study. We used baseline data of a RCT on the effectiveness and cost-effectiveness of physiotherapy in children with FC aged 4 to 17 years (Netherlands Trial Register, number 4797). Children diagnosed with FC by their general practitioner or pediatrician were included in that trial. Exclusion criteria for the RCT were children who had: 1) already received physiotherapy or urotherapy for FC in the past three years, 2) psychopathology affecting protocol adherence, and 3) serious or terminal illness. The RCT was approved by the Medical Ethical Board of the University Medical Center Groningen (number METc 2013/331. Both parents and child (if aged ≥ 12 years) provided informed consent to participate in the study.

For this agreement study only data of children aged 8 to 17 years were used, because children below eight years are too young to provide a self-report of their HRQoL.[10,15]

Measurements

HRQoL was measured with a disease specific questionnaire, the Defecation Disorder List (DDL) and a health status questionnaire, the Euroqol-5-Dimensions-Youth (EQ-5D-Y).[21-23] The questionnaires were completed both by the child and by one of the parents. Children and parents were instructed to fill in the questionnaires independently.

Disease specific Quality of Life

We used the emotional and social functioning subdomains of the Defecation Disorder List (DDL) as these two subdomains of the DDL measure HRQoL.[21, 22] These two subdomains of the DDL together consist of 25 statements, answered on a 5-point Likert scale, to indicate to what extent the user agrees with that statement. This corresponds with a score of 0, 25, 50, 75 or 100 points per statement. The (subdomain) scores are computed as the sum of the items divided by the number of items answered. The lowest possible score is 0 (poorest quality of life) and the maximum score 100 (best quality of life).

Health status

Of the Euroqol-5-Dimensions-Youth (EQ-5D-Y) the visual analogue scale (VAS) was used to measure health status.[23] The lowest possible score was 0 (worst health you can imagine) and the highest score was 100 (best health you can imagine).

Demographic and symptom related information

Demographic and health information, in particular age, gender, type of symptoms, duration and onset of symptoms and (information on) the use of laxatives, was assessed based on a questionnaire completed by the parents. Symptoms related to FC were assessed using a Dutch version of the 'Questionnaire on Pediatric Gastrointestinal Symptoms Rome-III' (QPGS-RIII).[24]

Statistical analysis

Appropriate descriptive statistics were used to present patient characteristics, symptoms of FC and the quality of life outcomes. Less than 1% of the statements on the DDL questionnaire remained unanswered (missing). The discrepancy scores (Δ) between parent-proxy and child-self reported HRQoL were calculated for all outcomes (DDL total score, DDL emotional and social subdomain scores and EQ-5D-Y-VAS score).
The level of parent-child agreement on HRQoL on group level was analyzed using intra-class correlation coefficients (ICC), using a two-way random model, single measures with absolute agreement. To indicate the level of agreement the conservative criteria of Portney and Watkins (2009) were used: an ICC of ≤ 0.75 is then classified as poor to moderate agreement; an ICC of 0.75-0.90 as good agreement; and an ICC of >0.90 as "reasonable agreement for clinical measurements".[25, 26]

Individual parent-child agreement was evaluated by visual inspection of the Bland-Altman plots. Perfect agreement between a child and a parent entails that the discrepancy score (Δ) is equal to zero. No systematic bias is assumed when the 95% confidence intervals around the mean discrepancy scores include zero. Limits of agreement were computed as follows: mean difference±1.96*standard deviation of the difference. Approximately 95% of the differences between child and parent reported HRQoL will lie between the limits of agreement.

In order to determine whether age and gender of the child influenced parent-child agreement we conducted multivariate linear regression analyses. Statistical analyses were performed using SPSS Version 24.0 (IBM corp., Armonk, New York, USA).

Sample size

An adequate sample size is important in order to obtain a reliable ICC parameter with

acceptable precision. When expecting an ICC of 0.8, using two observers per patient (child-report and parent proxy-report), and a 95%CI with a width of 0.2, a minimal sample size of 50 patients is required.[27] In addition, a sample size of approximately 50 patients is required to provide a reasonable number of dots in a Bland Altman plot to estimate the limits of agreement.[28]

Results

Participants

Among the 134 children participating in the RCT, 56 children fulfilled the inclusion criteria for this agreement study, i.e. were between 8 and 17 years of age. These were 24 boys and 32 girls, with a median age of 10 years (IQR 8 – 12). Patient characteristics are presented in Table 1. Disease specific HRQoL and health status of the children reported by the children and the parents are shown in Table 2.

Table 1. Baseline characteristics of the children aged 8 to 18 years with functional constipation diagnosed by their general practitioner or pediatrician (n = 56)

Age median (IQR) in years	10.0 (8.3–12.0)
Gender (% girls)	57.1
Duration of symptoms (n), months	
<3	8/50
3-12	6/50
>12	36/50
Abdominal pain/discomfort in the previous 4 weeks (n)	
Never	6/56
1–3 times a month	14/56
Once a week	7/56
Multiple times a week	21/56
Every day	8/56
FC symptoms (Rome-III criteria for FC) (n)	
<2 defecations in the toilet per week	14/56
Fecal incontinence >1 per week	16/56
Stool withholding	10/56
Painful or hard bowel movements	43/56
Large fecal mass in the abdomen or rectum	40/56
Large stools that obstruct the toilet	12/56
Use of laxatives in the previous 4 weeks (n)	
Yes	32/47
No	15/47
Previous episodes of FC (n)	
>2	34/52
1	2/52
0	16/52

FC = functional constipation; IQR = interquartile range; n = number.

Level of parent-child agreement

The mean discrepancy scores and the corresponding 95%CI intervals between child self and parent proxy-reports were for the DDL total score, DDL emotional functioning subdomain, DDL social functioning subdomain and EQ-5D-Y-VAS, -2.6 (-4.9 – -0.2), -2.2 (-5.2 – 0.7), -3.0 (-5.9 – 0.0), and -2.9 (-6.3 – 0.5), respectively. A negative score indicates that parents rated the HRQoL higher than the children did.

The level of parent-child agreement was good for the DDL total score (ICC: 0.80, 95%-CI 0.67–0.88), the DDL social functioning subdomain (ICC: 0.78, 95%-CI 0.65–0.87), and the EQ-5D-Y-VAS (ICC: 0.78, 95%-CI 0.65–0.88), and poor to moderate for the DDL emotional functioning subdomain (ICC: 0.73, 95%-CI 0.58–0.83) (Table 2).

Table 2. Disease-specific quality of life and health status of children with functional constipation (n = 56)

	Reported by		Results to evaluate absolute agreement		
	Children Median (IQR)	Parents Median (IQR)	Mean discrepancy score* (95% CI)	Limits of agreement	ICC (95% CI)
DDL total score	76 (65 – 84)	78 (67 – 85)	-2.6 (-4.9 to -0.2)	-19.7 – 14.6	0.80 (0.67 to 0.88)
DDL emotional functioning	72 (58 – 83)	75 (62 – 83)	-2.2 (-5.2 to 0.7)	-23.9 – 19.5	0.73 (0.58 to 0.83)
DDL social functioning	79 (64 – 89)	82 (65 – 89)	-3.0 (-5.9 to 0.0)	-24.2 – 18.3	0.78 (0.65 to 0.87)
EQ-5D-Y-VAS	84 (71 – 92)	85 (75 – 94)	-2.9 (-6.3 to 0.5)	-27.6 – 21.8	0.78 (0.65 to 0.87)

CI = confidence interval; DDL = Defecation Disorder List; EQ-5D-Y-VAS = Euroqol-5-Dimensions-Youth Visual Analogue Scale; ICC = Intraclass Correlation Coefficient; IQR = Inter Quartile Range.
*Discrepancy scores were calculated by subtracting each parent's score from their child's score. Negative differences indicate that parents evaluated the disease-specific quality of life and health status of their children better than the children did. Unlike the individual HRQoL scores reported by parents and children, the mean discrepancy scores were normally distributed in all outcome variables.

Bland-Altman plots are shown in Figure 1. Observed limits of agreement for the DDL total score were -19.7 and 14.6, for the emotional functioning subdomain -23.9 and 19.5, for the social functioning subdomain -24.2 and 18.3, and for the EQ-5D-Y-VAS -27.6 and 21.8. With a range on the scores between 0 and 100, the intervals between the limits of agreement showed that the level of agreement varied considerably between individual parent-child pairs.

Factors associated with parent child agreement

Multivariate linear regression analyses showed that age and gender of the child were not significantly associated with parent-child agreement for all outcomes (data not shown).

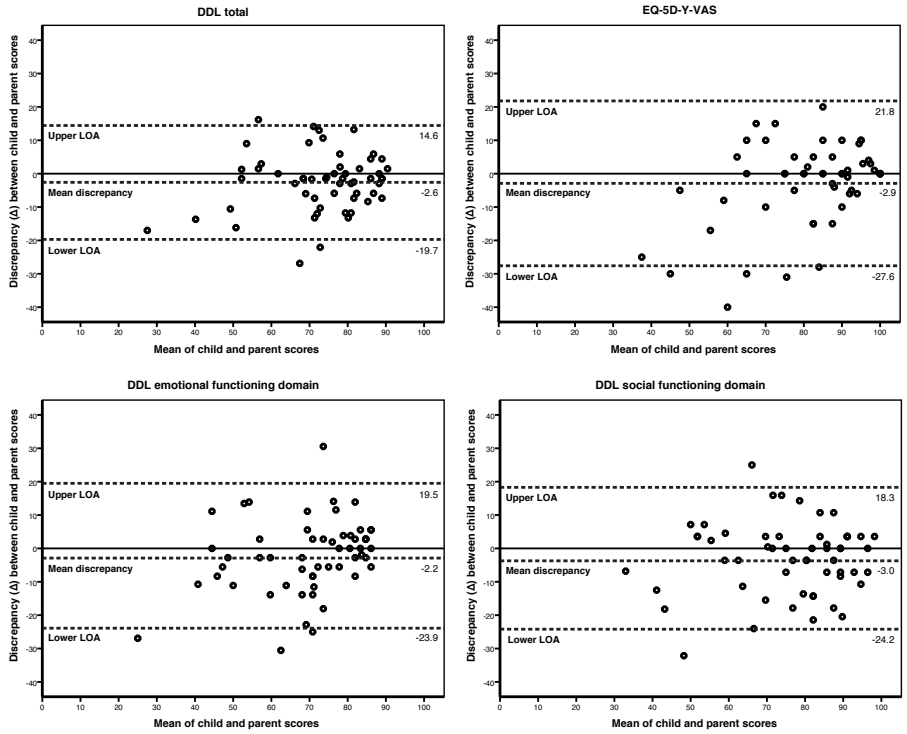


Figure 1. Bland-Altman plots. Top left: DDL total score, top right: EQ-5D-Y-VAS score, bottom left: DDL emotional functioning domain score, bottom right: DDL social functioning domain score. Discrepancy scores (D) were calculated by subtracting each parent's score from their child's score. DDL = Defecation Disorder List; EQ-5D-Y-VAS = Euroqol-5-Dimensions-Youth Visual Analogue Scale; LOA = Limits of Agreement.

Discussion

Main findings

This study showed that parent-child agreement on HRQoL in children with functional constipation was good on group level. In general, parents reported a minimally better disease specific HRQoL and health status than the children did. However, for individual child-parent pairs the level of agreement varied considerably. This is shown in the wide intervals between the limits of agreement, that were -19.7 and 14.6 (DDL total score,), and -27.6 and 21.8, (EQ-5D-Y-VAS). Therefore, it is sufficient to use only one report (parent or child which is more convenient), when one is interested in the HRQoL of a group of children with FC in primary care. However, when one is interested in the HRQoL of an individual child, we recommend to

use both reports. Age and gender of a child did not affect parent-child agreement on HRQoL in children with FC in primary care.

Comparison to literature

Consistent with our study, three other studies on FC, performed in a hospital setting, reported small mean discrepancy scores between child self and parent proxy reported HRQoL.[20,29,30] In our study parents were in general slightly more positive on the child's HRQoL. This overestimation of the child's HRQoL is in accordance to studies measuring parent-child agreement in healthy children.[10,13,17-19] In contrast, the three studies on parent-child agreement in a university hospital setting showed that parents were in general slightly more negative on the HRQoL of their child than the child was. Parents of children with other chronic conditions also tend to underestimate the child's HRQoL.[10,13,17-19] However, as stated before, on average the differences between parents and children were small.

Our findings of good parent-child agreement concerning HRQoL are consistent with another study in children with FC.[20] The level of parent-child agreement concerning HRQoL found in our study was better (ICCs between 0.73 and 0.80), than the parent-child agreement in the other study (ICCs between 0.55 and 0.74). Theoretically, these differences could be explained by either the other questionnaires that were used (DDL/EQ-5D-Y-VAS in this study vs PedsQL 4.0 Generic Core Scale in the other study), their clinical settings (primary care vs tertiary care) or the limitation of comparing ICCs for the level of parent-child agreement.[31]

Strengths and limitations

This is the first study examining agreement for HRQoL in children with FC for individual parent-child pairs. In addition, parent-child agreement was assessed for two different type of questionnaires measuring HRQoL, a disease-specific and a generic questionnaire. Disease specific instruments are more sensitive to detect small but relevant changes in the patient's HRQoL, while generic instruments are more useful to compare HRQoL across different patient groups.[32] By analyzing different aspects of agreement, such as by using discrepancy scores, ICCs, and Bland-Altman plots, our study attempts to comprehensively report on the nature of discrepancies between parent proxy and child self-reports concerning HRQoL in children with FC.

Our findings should be interpreted in the light of the following limitations. Parents and children have completed the questionnaires at home. The instruction was to complete the questionnaires independently. Although this study showed that the level of agreement between individual child-parent pairs varied considerably, there is a possibility that they

colluded, and therefore both parties might have given more moderate responses, which would enhance agreement and minimize differences.[17] Secondly, we did not collected demographic data of the parents. Thirdly, because of a limited sample size we only evaluated if age and gender of a child influenced parent-child agreement. We performed some hypothesize generating post hoc analyses but we found no indication that the number of Rome III criteria in a child, or separate Rome III criteria, influenced parent-child agreement on HRQoL (data not shown). In addition, there is limited knowledge about the psychometric properties of the DDL questionnaire. Finally, a limitation of the comparison of parent-child agreement using the ICC is that the ICC is an index of absolute agreement and consists of the ratio of between-subject variability and total variability.[31] Less heterogeneity in HRQoL scores between children may generate lower ICCs for parent-child agreement. In primary care children were seen with recent onset symptoms but also children with symptoms of longer duration. Therefore, it can be expected that there is much heterogeneity in HRQoL between children, which will lead to a better ICC. Thus, for the comparison of the level of parent-child agreement between studies, it is important to use several methods to evaluate agreement, i.e. discrepancy scores, ICCs, and Bland-Altman plots.

Implications for research

On a group level parent-child agreement concerning HRQoL was good. Therefore, in research focusing on group results, one can use either a parent-proxy report or a child-self report to assess HRQoL. For research looking at the individual patient's level, it is recommended to assess both the parent's, and the child's perception of the impact of the disease. More research into factors like severity of disease, duration of symptoms, parent-child relationship or mother or father's as proxy raters, that may influence parent-child agreement is needed. In addition, more research is needed into how and if a discrepancy between parent and child influence clinical decision making.

Implications for clinical practice

We found in our study that children and their parents may rate the impact of the FC on the quality of life of the child differently. Perceptions of the emotional impact of the FC may influence treatment adherence, as was found in a recent study.[6] Therefore, we advise clinicians to pay attention as well to the parent's perception of the child's HRQoL as to that of the child. A short question, like "we would like to know how good or bad your health is today on a scale from 0 to 100" which is used in the EQ-5D-Y-VAS, will be most suitable in clinical practice. However, as FC influenced especially the emotional and social aspects of HRQoL, the DDL questionnaire will be better in detecting relevant health issues of children with FC.[5]

References

1. Koppen IJN, Vriesman MH, Saps M, et al. Prevalence of Functional Defecation Disorders in Children: A Systematic Review and Meta-Analysis. J Pediatr. 2018 [epub ahead of print] doi: 10.1016/j.jpeds.2018.02.029.
2. Kovacic K, Sood MR, Mugie S, et al. A multicenter study on childhood constipation and fecal incontinence: effects on quality of life. J Pediatr. 2015;166(6):1482,1487
3. Rajindrajith S, Devanarayana NM, Weerasooriya L, et al. Quality of life and somatic symptoms in children with constipation: a school-based study. J Pediatr. 2013;163(4):1069,1072
4. Varni JW, Bendo CB, Nurko S, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. J Pediatr. 2015;166(1):85,90. e2.
5. Belsey J, Greenfield S, Candy D, et al. Systematic review: impact of constipation on quality of life in adults and children. Aliment Pharmacol Ther. 2010;31(9):938-49.
6. Koppen IJN, van Wassenaer EA, Barendsen RW, et al. Adherence to Polyethylene Glycol Treatment in Children with Functional Constipation Is Associated with Parental Illness Perceptions, Satisfaction with Treatment, and Perceived Treatment Convenience. J Pediatr. 2018 [Epub ahead of print] doi: 10.1016/j.jpeds.2018.03.066.
7. Tabbers MM, DiLorenzo C, Berger MY, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014 Feb;58(2):258-74.
8. Koppen IJN, Saps M, Lavigne JV, et al. Recommendations for pharmacological clinical trials in children with functional constipation: The Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterol Motil. 2018 Apr;30(4):e13294.
9. Davis E, Nicolas C, Waters E, et al. Parent-proxy and child self-reported health-related quality of life: using qualitative methods to explain the discordance. Quality of Life Research. 2007;16(5):863-71.
10. Matza LS, Swensen AR, Flood EM, et al. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value in health. 2004;7(1):79-92.
11. Ravens-Sieberer U, Erhart M, Wille N, et al. Generic health-related quality-of-life assessment in children and adolescents. Pharmacoeconomics. 2006;24(12):1199-220.
12. Wallander JL, Koot HM. Quality of life in children: a critical examination of concepts, approaches, issues, and future directions. Clin Psychol Rev. 2016;45:131-43.
13. Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Quality of life research. 2001;10(4):347-57.
14. Silva N, Crespo C, Carona C, et al. Why the (dis) agreement? Family context and child–

parent perspectives on health-related quality of life and psychological problems in paediatric asthma. Child: care, health and development. 2015;41(1):112-21.
15. Rebok G, Riley A, Forrest C, et al. Elementary school-aged children's reports of their health: a cognitive interviewing study. Quality of life research. 2001;10(1):59-70.
16. Riley AW. Evidence that school-age children can self-report on their health. Ambulatory Pediatrics. 2004;4(4):371-6.
17. Upton P, Lawford J, Eiser C. Parent–child agreement across child health-related quality of life instruments: a review of the literature. Quality of life research. 2008;17(6):895.
18. Galloway H, Newman E. Is there a difference between child self-ratings and parent proxy-ratings of the quality of life of children with a diagnosis of attention-deficit hyperactivity disorder (ADHD)? A systematic review of the literature. ADHD Attention Deficit and Hyperactivity Disorders. 2017:1-19.
19. Meyer M, Oberhoffer R, Hock J, et al. Health-related quality of life in children and adolescents: Current normative data, determinants and reliability on proxy-report. J Paediatr Child Health. 2016;52(6):628-31.
20. Hartman EE, Pawaskar M, Williams V, et al. Psychometric properties of PedsQL generic core scales for children with functional constipation in the Netherlands. J Pediatr Gastroenterol Nutr. 2014 Dec;59(6):739-47.
21. Voskuijl WP, van der Zaag-Loonen HJ, Ketel IJ, et al. Health related quality of life in disorders of defecation: the Defecation Disorder List. Arch Dis Child. 2004 Dec;89(12):1124-7.
22. Bongers ME, van Dijk M, Benninga MA, et al. Health related quality of life in children with constipation-associated fecal incontinence. J Pediatr. 2009;154(5):749,753.
23. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Quality of Life Research. 2010;19(6):875-86.
24. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006;130(5):1527-37.
25. Portney LG, Watkins MP. Foundations of clinical research: applications to practice. 3rd ed. Pearson Education; 2013.
26. Trevethan R. Intraclass correlation coefficients: clearing the air, extending some cautions, and making some requests. Health Serv Outcomes Res. 2017;17(2):127-43.
27. Giraudeau B, Mary J. Planning a reproducibility study: how many subjects and how many replicates per subject for an expected width of the 95 per cent confidence interval of the intraclass correlation coefficient. Stat Med. 2001;20(21):3205-14.
28. De Vet HC, Terwee CB, Mokkink LB, et al. Measurement in medicine: a practical guide. first ed. Cambridge: Cambridge University Press; 2011.
29. Youssef NN, Langseder AL, Verga BJ, et al. Chronic childhood constipation is associated with impaired quality of life: a case-controlled study. J Pediatr Gastroenterol Nutr.

2005;41(1):56-60.
30. Clarke MC, Chow CS, Chase JW, et al. Quality of life in children with slow transit constipation. J Pediatr Surg. 2008;43(2):320-4.
31. Crowley AL, Yow E, Barnhart HX, et al. Critical Review of Current Approaches for Echocardiographic Reproducibility and Reliability Assessment in Clinical Research. Journal of the American Society of Echocardiography. 2016;29(12):1144,1154. e7.
32. Brouwer CN, Maillé AR, Rovers MM, et al. Health-related quality of life in children with otitis media. Int J Pediatr Otorhinolaryngol. 2005;69(8):1031-41.

Chapter 6

Bladder Symptoms in Children With Functional Constipation: A Systematic Review

Jojanneke J.G.T. van Summeren, Gea A. Holtman, Sonja C. van Ommeren, Boudewijn J. Kollen, Janny H. Dekker, and Marjolein Y. Berger

J Pediatr Gastroenterol Nutr 2018; 67: 552-560

Abstract

Objective

The aim of the review is to perform a systematic review of the literature examining the prevalence of bladder symptoms in children with functional constipation (FC) and to compare the prevalence of those symptoms between children with and without FC.

Methods

In this systematic review 4 databases were searched to July 2018. Studies investigating the prevalence of bladder symptoms in children aged 4 to 17 years with FC were included. There was no language restriction. Two reviewers independently extracted data and assessed study quality. Clinical heterogeneity between studies was investigated. Prevalence rates of bladder symptoms in children with FC were calculated. Relative risks were calculated to compare the prevalence of bladder symptoms between children with and without FC.

Results

Among 23 studies of children with FC, 22 reported the prevalence bladder symptoms (12,281 children) and 7 reported the prevalence of urinary tract infections (UTIs) (687 children). The prevalence rates of single bladder symptoms, lower urinary tract symptoms (LUTS), and UTI varied between 2% to 47%, 37% to 64%, and 6% to 53%. The relative risks were 1.24 to 6.73 for 20 single bladder symptoms (12 studies) and 2.18 to 6.55 for UTI (2 studies). The 95% confidence intervals indicated significance in 14 of 20 single bladder symptoms.

Conclusions

Bladder symptoms seem common in children with FC, but the reported prevalence varies greatly. Children with FC are more likely to have bladder symptoms than children without FC. We recommend that clinicians be aware of concomitant bladder symptoms in children presenting with FC.

Introduction

Functional constipation (FC) is common among children.[1] Co-occurrence with bladder symptoms, such as lower urinary tract symptoms (LUTS) and urinary tract infection (UTI), is often reported.[2-5] The international Children's Continence Society (ICCS) has introduced the term bladder and bowel dysfunction (BBD) to emphasize the frequent combination of bladder and bowel problems.[6] Clinical experts have reported the prevalence of bladder symptoms as approximately 30% in children with FC,[4,7] though figures range from 12% to 46%.[8-11] Bladder and bowel problems, especially in combination, can lead to reduced psychosocial well-being and may have negative impact on bladder and renal function.[12-15] Focusing on one condition may lead to inadequate diagnostic and therapeutic interventions.

The explanation of the frequent co-occurrence of bowel and bladder dysfunction is that they share a common pathway. The underlying pathophysiology of this common pathway is not completely understood, but two main pathways are assumed. First, there may be a mechanical problem, with the proximity of the bladder and bowel meaning that large volumes of feces in the rectum could place direct pressure on the posterior bladder wall, which in turn, may cause bladder emptying and storage problems.[3,16] Second, there may be a neurogenic problem. The genito-urinary tract and gastrointestinal system share the same embry-ologic origin in the hindgut. Given that normal functioning of the pelvic organ systems requires cross-sensitization between neural pathways, dysfunction of 1 of the 2 organ systems could lead to dysfunction of the other.[17,18]

Little is known about the actual extent of bladder symptoms in children with FC. In this study, we therefore aimed to conduct a systematic review of studies on the prevalence of bladder symptoms in children with FC. The secondary aim was to compare this prevalence among children with and without FC.

Methods

Search Strategy

A systematic literature search was conducted of the MEDLINE, EMBASE, PsycINFO, and Cochrane library electronic databases (from January 1990 to July 17, 2018), using Medical Subject Headings, Emtree terms, and free text words related to child, FC, and bladder symptoms (LUTS and UTI) (Supplemental Content 1). In addition, experts were consulted, and a clinical librarian assisted in the literature search. No language restrictions were applied. The protocol of the systematic review has been published in the International Prospective

Register of Systematic Reviews (number PROSPERO 2016:CRD42016045742).

Study Selection

The population of interest was children aged 4 to 17 years with FC, and we used the definitions of conditions applied by the authors of each article. Studies of children with underlying organic or metabolic causes of constipation, or with psychological or behavioral problems known to be related to either FC or LUTS or UTI, were excluded. The conditions of interest were bladder symptoms and UTI. Studies that reported on the prevalence of bladder symptoms or UTI in children with FC, or that provided enough information to allow us to calculate this prevalence, were eligible for inclusion. All clinical settings (contexts) were included (ie, community, primary care, and specialist care populations).

Two reviewers (J.V.S. and S.V.O.) independently screened the titles and abstracts of all identified articles, before assessing the full text of identified articles for potential inclusion. Disagreement was resolved through discussion with a third reviewer (J.D.). Also, the reference lists of selected full-text articles and review articles were hand-searched by the two authors.

Quality Assessment

The quality of the included studies was assessed using a critical appraisal checklist for prevalence studies (Supplemental Content 2).[19] This instrument contained 9 items addressing the following: sample adequacy; sample frame bias; sample size adequacy (5% precision); appropriateness of study subjects and setting description; missing at random data; consistency of bladder symptoms descriptions with the ICCS terminology document (validity); assessment bias; prevalence with confidence intervals (CIs); and whether the response rate with refusals was described.[20] We assessed each item as having risk of bias, no risk of bias, or unclear risk of bias. Quality assessment focused only on the study elements relevant to estimate the prevalence and was done by two reviewers independently (J.V.S. and G.H.), with any disagreement resolved through discussion with a third reviewer (M.B.).

Data Extraction

Data extraction was performed independently by 2 researchers (J.V.S. and S.V.O.), using a structured data extraction form, with disagreement resolved through discussion with a third reviewer (J.D.). The following data were extracted: general study information, population characteristics (eg, number of participants with FC, age, gender, definition, and method of data collection for FC, and if specified, the number of control children without FC), condition characteristics (eg, definitions and method of data collection for bladder symptoms and UTI), and context characteristics (eg, setting, and recruitment of patients).

Data Synthesis and Analysis

Point or period prevalence rates were defined as the proportions of children with bladder symptoms and/or UTI in a population of children with (or without) FC at a specific point in time or within a defined period, respectively. The prevalence and corresponding 95% CIs were presented in a forest plot. If at least 4 suitable studies were available for analysis, we intended to perform a meta-analysis in homogeneous populations of children based on population characteristics (ie, definition of FC), condition characteristics (ie, definition of bladder symptoms or UTI), and setting. Forest plots were produced for prevalence using the ''metaprop cinmethod(exact)'' command in STATA/SE version 14 (Stata Corp, College station, TX).[21]

To evaluate the association between bladder symptoms and FC, we selected studies reporting the prevalence of bladder symptoms and UTI in children with and without FC. Relative risks (RRs) and corresponding 95% CIs were calculated with 2x2 tables and presented in a forest plot. Statistical significance was accepted when the 95% CI did not include 1. Forest plots of RRs were produced using Review Manager 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark).

Results

Study Selection

A flowchart of the screening and selection process of the studies is shown in Figure 1. We included 23 studies, among which 22 reported the prevalence of at least 1 bladder symptom[8-11,22–39] and 7 reported the prevalence of UTIs.[8,11,28,32,34,35,40]

Quality Assessment

We evaluated the methodological quality of the studies as their ability to find valid and unbiased estimates of the prevalence of bladder symptoms and UTI. The quality of the selected studies was rated as poor to moderate (Table 1). Sample adequacy was addressed for bladder symptoms in 18 of 22 studies[8–11,23–27,30,33–39] and for UTI in 1 of 7 studies.[8] In 15 of 23 studies,[8–10,22–24,26,29,31,33,36–40] a random or consecutive sample of participants was recruited, and in 11 of 23 studies the response rate with refusals was adequate (>70%) or appeared to be unrelated to the outcome.[9,22,24,25,27,29–31,36,40]

Table 1. Methodological Assessment of the Included Studies

Studies	1 Was the Sample Frame Appropriate to Address The Target Population?*	2 Were Study Participants Recruited in an Appropriate Way?	3 Was the Sample Size Adequate?	4 Were the Study Subjects and the Setting Described in Detail?	5 Was the Data Analysis Conducted With Sufficient Coverage of the Identified Sample?	6 Were Valid Methods Used for the Identification of the Condition?*	7 Was the Condition Measured in a Standard, Reliable Way for All Participants?*	8 Was There Appropriate Statistical Analyses?*	9 Was the Response Rate Adequate, and if Not, Was the Low Response Rate Managed Appropriately?
General population									
Chung 2010	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	No	Yes
Esezobor 2016	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes
Hamed 2017	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear
Kajiwara 2004	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Kajiwara 2006	Yes	Yes	No	Yes	Unclear	Yes	Yes	No	No
Kalo 1996	Yes	Unclear	No	Yes	Yes	Yes	Yes	Yes	Yes
Sampaio 2016	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Unclear
Sarici 2016	Yes	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No
Söderstrom 2004	Yes	Yes	No	Yes	Unclear	Yes	Yes	No	No
Uguralp 2003	Yes	No	No	Yes	Unclear	Yes	Yes	Yes	Yes
Primary care									
Loening-Baucke 2007	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes
Specialty care									
Van Engelenburg, van Lonkhuyzen, 2016†	No	Unclear	No	Unclear	Unclear	Yes (bladder symptoms) Unclear (UTI)	Unclear	Yes	No
McDonald 2004	No	Yes	No	Yes	Unclear	Yes	Unclear	Yes	Yes
Reich 2010‡	No	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes
Clavero 1993	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Dehghani 2013†	Yes	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear
Dijk, van 2010	Yes	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Yes
Foreman 1996	No	Yes	No	Yes	No	Yes	Unclear	Yes	Yes
Hadjizadeh 2009†	No	Unclear	No	Yes	Unclear	Yes	Yes	Yes	Unclear
Imanzadeh 2013	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear	Yes	Unclear
Karakelleoglu 1997†	Yes (bladder symptoms) No (UTI)	Unclear	No	Yes	Unclear	Yes	Unclear (bladder symptoms) Yes (UTI)	Yes	Unclear
Kasirga 2006†	Yes (bladder symptoms) NO (UTI)	Unclear	No	No	Unclear	Yes	Unclear (bladder symptoms) Yes (UTI)	Yes	Unclear
Loening-Baucke 1997†	Yes	Yes	No	Yes	Unclear	Yes	Unclear (bladder symptoms) Yes (UTI)	Yes	Unclear

''Yes'' means an adequate score, ''no'' means an inadequate score, and ''unclear'' means the study authors provided either no information or incomplete information.
*Questions 1, 5, 7, and 8 were scored separately for the outcomes bladder symptoms and UTI. Where discrepancies occurred between the bladder symptoms and UTI score, both are shown in brackets with the outcome.
†These studies give the prevalence of both bladder symptoms and UTIs.
‡This study only give the prevalence of UTI, all other studies give only the prevalence of bladder symptoms.UTI = urinary tract infection.

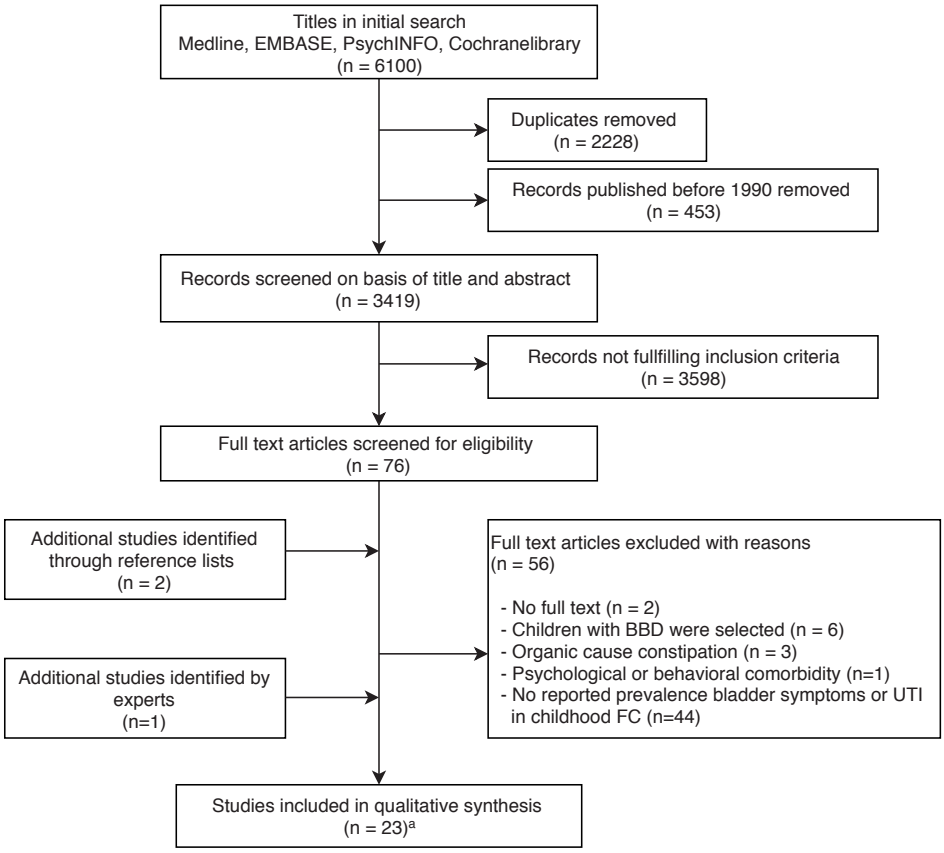


Figure 1. Flowchart of the study screening and selection process. *In children with FC, 22 studies reported the prevalence of LUTS (n= 12, 281, range 30–8219) and 7 reported the prevalence of UTI (n=687, range 31–234). FC = functional constipation; LUTS = lower urinary tract symptoms; UTI = urinary tract infection.

Description of Selected Study Populations

The characteristics of the included studies are summarized in Supplemental Content 3. The definition of FC was reported according to the Rome III criteria for FC in 5 studies,[10,11,28,36,40] to another described definition in 12 studies,[9,22–24,27,30,32–35,37,39] and to no described definition in six 6 studies.[8,25,26,29,31,37] A validated or a modified version of the dysfunctional voiding symptom score (DVSS) was used in three studies.[10,22,32] Urinary incontinence (UI) was measured in 20 studies: in 6 the frequency of urine leakage was at least once a week[8–10,27,29,36]; in 4 the frequency of urine leakage was at least once a month[24–26,38]; and in 10, the frequency of urine leakage was not reported.[11,28,30–35,37,39] Finally, UTI was diagnosed by urinalysis and culture in 6 studies,[8,11,32,34,35,40] and in 1 study, the authors did not describe how they diagnosed UTI.[28] Ten studies were conducted in a community population,[10,22–27,36–38] 1 in

a primary care population,[9] and 12 in specialist care.[8,11,28–35,39,40]

The significant differences in populations (FC definition), conditions (definition of bladder symptoms), and settings meant that a meta-analysis of the reported prevalence and RRs would be inappropriate and meaningless.[19]

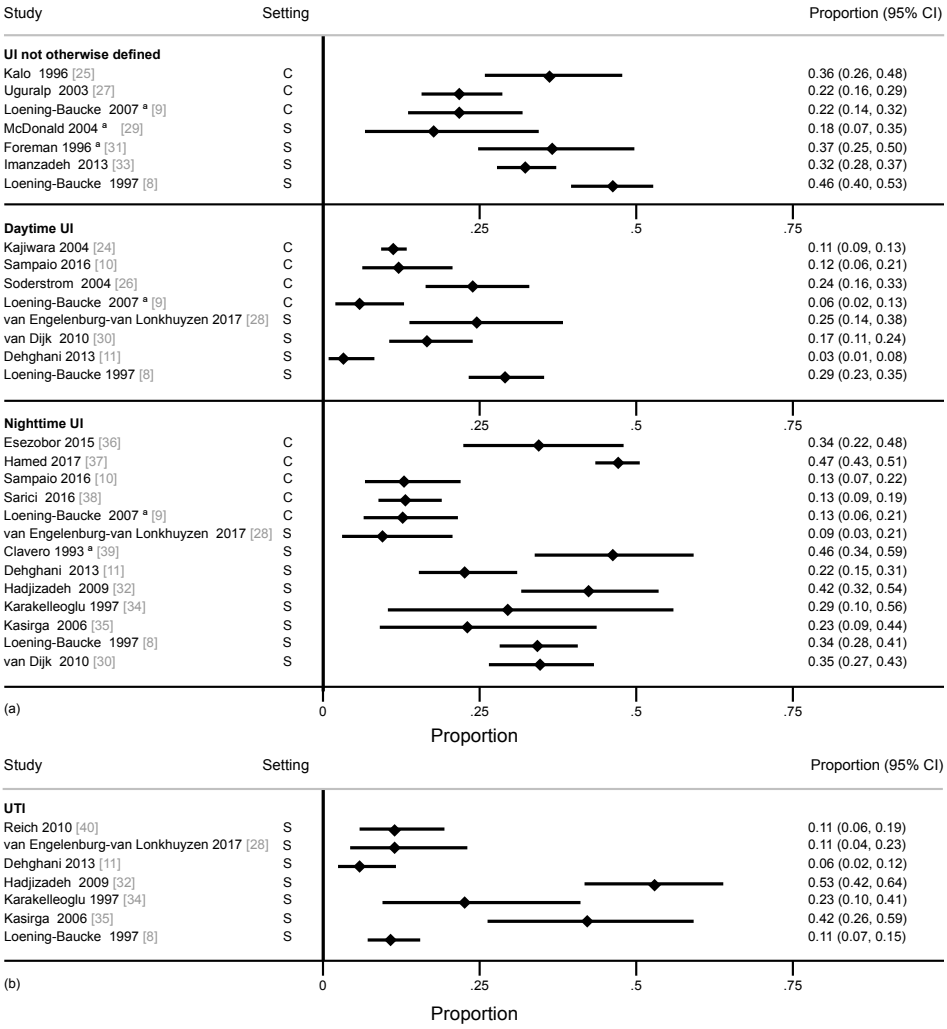


Figure 2. Prevalence and 95% CI of UI and UTI in children with FC. A, Proportion and 95% CI for UI not otherwise defined, daytime UI, and nighttime UI. B, Proportion and 95%CI for UTIs. *These studies estimated a period prevalence of UI instead of a point prevalence for either 6 months,[9] 4 months[29] or an undocumented period.[31,39] C = community or primary care population; FC = functional constipation; S = specialist care population; UI = urinary incontinence; UTI = urinary tract infection.

Prevalence of Bladder Symptoms in Children With Functional Constipation

Four studies on UI reported the period prevalence,[9,29,31,39] and all other studies reported point prevalence (Figure 2). The prevalence of LUTS (based on the DVSS) was reported in 3 studies as 37% (95% CI 36% – 38%),[22] 39% (95% CI 27% – 52%),[10] and 64% (95% CI, 52% – 74%).[32]

The prevalence for UI not otherwise defined ranged between 18% and 46%,[9,25,27,29,31,33,36,41] for daytime UI between 3% and 29%,[9,11,24,26,28,30,41] and for nighttime UI between 13% and 47% (Figure. 2a).[9–11,28,30,32,34,35,37–39,41] The prevalence of other bladder storage symptoms was as follows: overactive bladder, 19% (95%CI 11 – 31%)[23]; decreased frequency of micturition, 20% (95% CI 12%–29%)[10]; increased frequency of micturition, 13% (95% CI 7% – 20%)[11]; urgency, 25% (95% CI 17% – 35%) in 1 study[10] and 27% (95% CI 12%–48%) in another[35]; and urge UI, 19% (95% CI 7%–39%).[35] For bladder voiding symptoms, the prevalence was as follows: dysuria, 10% (95% CI 5% – 18%)[10] and 17% (95% CI 10% – 25%)[11]; and straining, 2% (95% CI 0% – 8%).[10] For other bladder symptoms, the prevalence of dribbling was 4% (95% CI 1%–6%)[11] and the prevalence of holding maneuvers was 49% (95% CI 39% – 60%).[10]

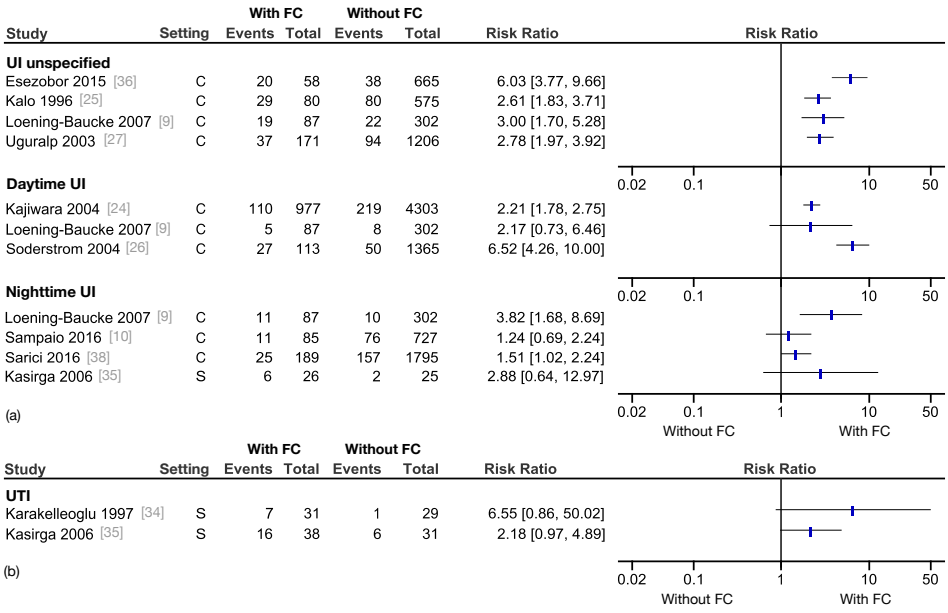


Figure 3. RR and 95% CI for UI and UTI in children with and without FC. A, RR and 95% CI for UI not otherwise defined, daytime UI, and nighttime UI. B, RR and 95% CI for UTIs. C = community or primary care population; FC = functional constipation; RR = relative risk; S = specialist care population; UI = urinary incontinence; UTI = urinary tract infection.

Prevalence of Urinary Tract Infections in Children With Functional Constipation

No studies reported a period prevalence or incidence of UTI. The prevalence of UTI in children with FC was only measured once at enrollment in all studies, and ranged between 6% and 53% (Figure 2B).[8,11,28,32,34,35,40]

Relative Risk for Bladder Symptoms and Urinary Tract Infection in Children With and Without Functional Constipation

In 12 of 23 studies, bladder symptoms were also observed in children without FC (Figure 3A).[9,10,23–27,32,35–38] Children without FC were recruited in the same community (10 studies), in 1 study the control group consisted of children consulting the pediatrician with other than gastrointestinal or urological symptoms, and in 1 study the control group consisted of volunteers without gastrointestinal diseases in history. The RRs for LUTS were 4.54 (95% CI 3.08 – 6.71)[10] and 6.35 (95% CI 4.32 – 6.71),[32] and the results were statistically significant.

For UI not otherwise defined the RRs were between 2.61 and 6.03 (4 studies, 95% CI 1.70–9.66), and all RRs were statistically significant (9,25,27,36). The RRs for daytime UI were between 2.17 and 6.52 (3 studies, 95% CI 0.73 – 10.00) (9,24,26), but only 2 RRs were statistically significant (24,26). The RRs for nighttime UI were between 1.24 and 3.82 (4 studies, 95% CI 0.64 – 12.97) (9,10,35,38), but again, only 2 RRs were statistically significant (9,38). In a fifth study, we identified an unexplainable but very high RR of nighttime UI (38.58; 95% CI 28.67 – 51.90) (37). We decided to report this study as an outlier, and therefore, it was not included in the reporting on nighttime UI (Figure 3A).

The RRs for bladder storage symptoms were as follows: overactive bladder, 1.46 (95% CI 0.76 – 2.79)[23]; decreased micturition, 3.85 (95% CI 2.29 – 6.45)[10]; and urgency, 6.73 (95% CI 0.89 – 50.84)[35] and 1.57 (95% CI 1.06 – 2.32).[10] The RRs for bladder voiding symptoms were 4.87 (95% CI 2.20– 10.81) for dysuria[10] and 2.71 (95% CI 0.55–13.21)[10] for straining. For holding maneuvers the RR was 2.05 (95% CI 1.61– 2.62).[10]

The prevalence of UTI was only reported for children without FC in 2 of the 7 studies covering UTI (Figure 3B). The RRs were 2.18 (95% CI 0.97–4.89)[35] and 6.55 (95% CI 0.86–50.02)[34] for these studies, but neither was statistically significant.

Discussion

To the best of our knowledge, this is the first systematic review of studies reporting the prevalence of bladder symptoms in children with FC. The prevalence of LUTS was 37% to 64% in 3 studies of children with FC, though the prevalence of single bladder symptoms ranged from 2% to 47% in the 22 studies. Among these, UI was the most evaluated bladder symptom (21 studies), with a reported prevalence of 3% to 47%. Clinical heterogeneity in the definitions of bladder symptoms and FC between studies meant that we could not statistically pool the prevalence.

Among the included studies, bladder symptoms occurred more frequently in children with FC than in children without FC, though the RR had wide ranges. The RRs for both studies of LUTS were statistically significant at 4.54 and 6.35, but the RRs for single bladder symptoms ranged from 1.24 to 6.73 among 18 studies, of which 6 were not significant. Therefore, our results indicate that children with FC are more likely to have bladder symptoms than children without FC, which supports the assumption of a common pathway for FC and LUTS.[2–5] One study showed a very high RR (38.58; 95% CI 28.67 – 51.90) of nighttime UI in children with FC compared to children without FC.[37] Characteristics like age, definition of FC and context cannot explain this outlier. One study not included in this systematic review investigated the co-occurrence of bladder symptoms and FC in consultations. In this Australian study, pediatricians have recorded all clinical problems for 4181 consultations in 2013. In 212 (5%) of the consultations FC was reported and among 52 (24.5%) of these consultations nighttime UI was reported.[42]

By contrast, although 7 studies reported that prevalence of UTI in children with FC was 6% to 53%, only two small studies compared the prevalence of UTI between children with and without FC. This was insufficient to do any meaningful analysis on the association between FC and UTI.

Methodological Issues With the Prevalence Studies

For an accurate evaluation of prevalence, two methodological questions need to be answered: '1) How representative are the patients recruited in the included studies for the target population?' and '2) Are the outcome measures valid and reliable?',[43] In our review, the target population was defined as children aged 4 to 17 years who had FC, and the outcome measures were bladder symptoms and UTI.

In 4 of the 22 studies measuring bladder symptoms the patients did not represented

the target population exactly. These studies either included only boys,[31] or excluded children belonging to our target population (ie, excluding children with earlier treatment for BBD).[22,28,29,31] In addition, not all studies included a random or consecutive sample of patients, or examined selective inclusion due to non-response. Therefore, care should be taken when extrapolating the prevalence of bladder symptoms, which certainly cannot be averaged.

The methods used to measure bladder symptoms and UTI varied between studies, thereby possibly affecting the prevalence. In 2006 (updated in 2016) the ICCS agreed criteria for diagnosing bladder symptoms.[6,44] According to the ICCS, UI is defined as involuntary urine leakage on a regular basis in a child aged 5 years and older. The studies in this review used different frequencies of urine leakage (from at least weekly to at least monthly). Thus, studies that included involuntary urine leakage at least once per month might have overestimated the prevalence of UI in comparison with studies that included involuntary urine leakage as once a week.

No studies measured the period prevalence of UTI. Given that UTI can be recurrent, though mostly limited in time, the true prevalence will probably be underestimated when using point prevalence. In addition, 6 out of 7 studies measuring UTI included children under the age of 4 years and all studies were performed in specialist care. It is unknown whether the reported prevalence rates of UTI can be extrapolated to children aged 4 to 18 years with FC.

Finally, only 6 studies had sufficiently large sample sizes to calculate prevalence estimates with a 5% precision. Thus, the prevalence estimates of these studies lacked precision.[45,46]

Strengths and Limitations

We applied a broad search strategy and also included studies in which the main aim was not to evaluate the prevalence of bladder symptoms in children with FC. An additional 2 studies were found via reference lists. Therefore, we are confident that we did not miss relevant studies. The prevalence of FC in children with bladder symptoms felt outside the scope of this study. When selecting eligible studies, we did not apply any restrictions to the definition of FC, instead aiming to include a representative sample of children with FC. An obvious drawback of this approach is that the heterogeneity of results increases. Only 5 studies used the advocated Rome criteria to define FC.[10,11,28,36,40] Clinicians and researchers (especially in older studies) often use less well-defined criteria for diagnosis. In five studies FC was defined as encopresis or fecal incontinence.[25,26,29,31,39] The definitions of FC and bladder symptoms were more in line with each other if they were performed in the same clinical setting. This makes a comparison between different clinical settings even more complicated. Due to

the limited number of studies conducted in clinically homogeneous populations, according to setting, definition of FC and definition of bladder symptoms, we could not give pooled prevalence rates or pooled RRs.

Clinical Implications

FC appears to increase the risk of bladder symptoms in children aged 4 to 17 years. Despite expert reports that the prevalence of LUTS is approximately 30% in children with FC,[4,7] our review indicates that this might underestimate the true prevalence. Indeed, we found that the prevalence of LUTS was 37% to 64%. The early diagnosis and treatment of bladder problems in children with FC is considered essential to preventing adverse effects on kidney function, bladder function, and psychosocial well-being.[12,13] The propensity for clinicians to underdiagnose BBD was also highlighted in a study in which parents reported more concomitant bladder and bowel problems than clinicians did, regardless of the healthcare setting.[47] Therefore, we recommend that clinicians be aware of concomitant bladder problems in children presenting with FC.

Constipation management is the first step of treatment in children with BBD, as relief of bowel dysfunction has been shown to reduce the frequency of UI.[8,48] During evaluation of treatment, disappearance of both constipation symptoms and bladder symptoms have to be monitored. Children with FC and bladder symptoms can be treated in primary care or by a general pediatrician. Consider referral to a specialist when no or only partial response of adequate constipation management is achieved after 6 months.[12]

Recommendations for Further Research

More research is needed in less clinically heterogeneous populations to clarify the true prevalence of bladder symptoms and UTI in children with FC. Future studies should use consistent diagnostic frameworks to further reduce heterogeneity and facilitate future meta-analysis. In addition, it would be interesting to investigate if the prevalence of bladder symptoms is influenced by the type of FC: functional fecal retention and slow-transit constipation or by behavioral or psychological comorbidity.[49,50]

Secondly, future research should seek to unravel the association between FC and either bladder symptoms or UTI by age and the severity and duration of FC symptoms. Lastly, the common pathway theory suggests that we need to adopt a simultaneous approach to the treatment of bladder and bowel problems.[3,7,16] Future research must investigate how interventions directed at both conditions affect prognosis.[3,7,16]

Conclusions

Given the findings of this study, we cannot make any definitive statements on the prevalence of bladder symptoms in children with FC. This is hampered by the wide variation in prevalence, despite bladder symptoms clearly occurring with significant frequency in children with FC. Indeed, our review indicates that children with FC are more likely to have bladder symptoms than are children without FC. Until more robust data can be presented, it is important for clinicians to be alert for concomitant bladder symptoms in children consulting with FC. Early diagnosis and treatment are straightforward and can have marked beneficial effects on prognosis and psychosocial well-being.

References

1. Koppen IJN, Vriesman MH, Saps M, et al. Prevalence of functional defecation disorders in children: a systematic review and meta-analysis. J Pediatr 2018;199:212 – 6.
2. Rasquin A, Di Lorenzo C, Forbes D, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006; 130:1527 – 37.
3. Rajindrajith S, Devanarayana NM, Perera BJC, et al. Childhood constipation as an emerging public health problem. World J Gastroenterol 2016;22:6864.
4. Benninga MA, Voskuijl WP, Taminiau J. Childhood constipation: is there new light in the tunnel? J Pediatr Gastroenterol Nutr 2004; 39:448 – 64.
5. Van Den Berg, Maartje M, Benninga M, et al. Epidemiology of childhood constipation: a systematic review. Am J Gastroenterol 2006; 101:2401 – 9.
6. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the International Children's Continence Society. Neurourol Urodyn 2016;35:471 – 81.
7. Burgers R, de Jong TP, Visser M, et al. Functional defecation disorders in children with lower urinary tract symptoms. J Urol 2013;189:1886 – 91.
8. Loening-Baucke V. Urinary incontinence and urinary tract infection and their resolution with treatment of chronic constipation of childhood. Pediatrics 1997;100 (2 pt 1):228–32.
9. Loening-Baucke V. Prevalence rates for constipation and faecal and urinary incontinence. Arch Dis Child 2007;92:486 – 9.
10. Sampaio C, Sousa AS, Fraga LGA, et al. Constipation and lower urinary tract dysfunction in children and adolescents: a population-based study. Front Pediatr 2016;4:101.
11. Dehghani SM, Basiratnia M, Matin M, et al. Urinary tract infection and enuresis in children with chronic functional constipation. Iran J Kidney Dis 2013;7:363 – 6.
12. Dos Santos J, Lopes RI, Koyle MA. Bladder and bowel dysfunction in children: an update on the diagnosis and treatment of a common, but underdiagnosed pediatric problem. Can Urol Assoc J 2017;11: S64 – 72.
13. Bower WF. Self-reported effect of childhood incontinence on quality of life. J Wound Ostomy Continence Nurs 2008;35:617 – 21.
14. Brownrigg N, Braga L, Rickard M, et al. The impact of a bladder training video versus standard urotherapy on quality of life of children with bladder and bowel dysfunction: a randomized controlled trial. J Pediatr Urol 2017;13:374.e1 – 8.e8.
15. Kovacic K, Sood MR, Mugie S, et al. A multicenter study on childhood constipation and fecal incontinence: effects on quality of life. J Pediatr 2015;166:1482.e1 – 7e.

16. Averbeck MA, Madersbacher H. Constipation and LUTS: how do they affect each other? Intl Braz J Urol 2011;37:16–28.
17. Malykhina A. Neural mechanisms of pelvic organ cross-sensitization. Neuroscience 2007;149:660–72.
18. Kaplan S, Dmochowski R, Cash B, et al. Systematic review of the relationship between bladder and bowel function: implications for patient management. Int J Clin Pract 2013;67:205–16.
19. Munn Z, Moola S, Lisy K, et al. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc 2015;13:147 – 53.
20. Gordon N. A question of response rate. Science 2002;25:25.
21. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. Arch Public Health 2014;72:39.
22. Chung JM, Lee SD, Kang DI, et al. An epidemiologic study of voiding and bowel habits in Korean children: a nationwide multicenter study.Urology 2010;76:215–9.
23. Kajiwara M, Inoue K, Mutaguchi K, et al. The prevalence of overactive bladder and nocturnal enuresis in Japanese early adolescents: a questionnaire survey. Hinyokika Kiyo 2006;52:107–11.
24. Kajiwara M, Inoue K, Usui A, et al. The micturition habits and prevalence of daytime urinary incontinence in Japanese primary school children. J Urol 2004;171:403–7.
25. Kalo BB, Bella H. Enuresis: prevalence and associated factors among primary school children in Saudi Arabia. Acta Paediatr 1996;85:1217-22.
26. Söderstrom U, Hoelcke M, Alenius L, et al. Urinary and faecal incontinence: a population-based study. Acta Paediatr 2004;93:386 – 9.
27. Uguralp S, Karaoglu L, Karaman A, et al. Frequency of enuresis, constipation and enuresis association with constipation in a group of school children aged 5-9 years in Malatya, Turkey. Turk J Med Sci 2003;33:315 – 20.
28. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, et al. Effectiveness of pelvic physiotherapy in children with functional constipation compared with standard medical care. Gastroenterology 2017;152:82 – 91.
29. McDonald LA, Rennie AC, Tappin DM. Constipation and soiling— outcome of treatment at one year. Scott Med J 2004;49:98 – 100.
30. van Dijk M, Benninga MA, Grootenhuis MA, et al. Prevalence and associated clinical characteristics of behavior problems in constipated children. Pediatrics 2010;125:e309 – 17.
31. Foreman DM, Thambirajah MS. Conduct disorder, enuresis and specific developmental delays in two types of encopresis: a case-note study of 63 boys. Eur Child Adolesc Psychiatry 1996;5:33 – 7.

32. Hadjizadeh N, Motamed F, Abdollahzade S, et al. Association of voiding dysfunction with functional constipation. Indian Pediatr 2009;46:1093 – 5.
33. Imanzadeh F, Sayyari AA, Sharifian M, et al. Is there a relationship between constipation and time of enuresis: single center study in referral hospital, Tehran. Prz Gastroenterol 2013;8:176 – 9.
34. Karakelleoglu C, Orbak Z, Sen B, et al. Ultrasonographic evaluation of urinary tract in children with chronic functional constipation. Turk J Pediatr 1997;39:511 – 7.
35. Kasirga E, Akil I, Yilmaz O, et al. Evaluation of voiding dysfunctions in children with chronic functional constipation. Turk J Pediatr 2006; 48:340 – 3.
36. Esezobor C, Balogun M, Ladapo T. Prevalence and predictors of childhood enuresis in southwest Nigeria: findings from a cross-sectional population study. J Pediatr Urol 2015;11:338.e1 – 338.6.
37. Hamed A, Yousf F, Hussein MM. Prevalence of nocturnal enuresis and related risk factors in school-age children in Egypt: an epidemiological study. World J Urol 2016;35:1 – 7.
38. Sarici H, Telli O, Ozgur BC, et al. Prevalence of nocturnal enuresis and its influence on quality of life in school-aged children. J Pediatr Urol 2016;12:159e6.
39. Clavero Arevalo M, Toro Trallero J. Enuresis and encopresis: their relationship. An Esp Pediatr 1993;39:320 – 4.
40. Reich M, Iwańczak B. Symptoms associated with functional constipations in children and adolescents. Adv Clin Exp Med 2010;19: 519 – 30.
41. Loening-Baucke V, Cruikshank B, Savage C. Defecation dynamics and behavior profiles in encopretic children. Pediatrics 1987;80:672–9.
42. De S, Teixeira-Pinto A, Sewell JR, et al. Prevalence, patient and consultation characteristics of enuresis in Australian paediatric practice. J Paediatr Child Health 2018;54:620 – 4.
43. Boronat AC, Ferreira-Maia AP, Matijasevich A, et al. Epidemiology of functional gastrointestinal disorders in children and adolescents: a systematic review. World J Gastroenterol 2017;23:3915.
44. Neveéus T, von Gontard A, Hoebeke P, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006;176: 314 – 24.
45. Naing L, Winn T, Rusli B. Practical issues in calculating the sample size for prevalence studies. Arch Orofac Sci 2006;1:9 – 14.
46. Daniel WW, Cross CL. Determination of sample size for estimating proportions. In: Daniel WW, Cross CL, eds. Biostatistics: a Foundation for Analysis in the Health Sciences. New York, NY: John Wiley & Sons; 2013:191 – 3.
47. van Engelenburg-van Lonkhuyzen ML, Bols EM, Benninga MA, et al. Bladder and bowel

dysfunctions in 1748 children referred to pelvic physiotherapy: clinical characteristics and locomotor problems in primary, secondary, and tertiary healthcare settings. Eur J Pediatr 2017;176:207 – 16.

48. Borch L, Hagstroem S, Bower WF, et al. Bladder and bowel dysfunction and the resolution of urinary incontinence with successful management of bowel symptoms in children. Acta Paediatrica 2013:102.
49. Hyams JS, Di Lorenzo C, Saps M, et al. Childhood functional gastrointestinal disorders: child/adolescent Gastroenterology 2016;150: 1456.e2 – 68.e2.
50. Zivkovic VD, Lazovic M, Stankovic I, et al. Scintigraphy evaluation of the types of functional constipation in children with bowel bladder dysfunction. J Pediatr Urol 2014;10:1111–6.

Supplemental Content 1

PubMed

("Constipation"[Mesh] OR constipat*[tiab] OR obstipat*[tiab] OR bladder and bowel dysfunction*[tiab] OR dysfunctional elimination syndrome*[tiab] OR encopres*[tiab] OR ((faecal[tiab] OR fecal[tiab] OR rectal[tiab] OR rectum[tiab] OR imcomplet*[tiab] OR incomplet*[tiab]) AND (impact*[tiab] OR evacuat*[tiab])) OR defecat*[tiab] OR defaecat*[tiab] OR stool*[tiab] OR ((bowel[tiab] OR abdom*[tiab]) AND (function*[tiab] OR habit*[tiab] OR movement*[tiab] OR symptom*[tiab] OR motion*[tiab])))

AND

("Lower Urinary Tract Symptoms"[Mesh] OR "Enuresis"[Mesh] OR "Urinary Incontinence"[Mesh] OR "Urination"[Mesh] OR "Urinary Bladder"[Mesh] OR "Oliguria"[Mesh] OR "Urinary Retention"[Mesh] OR ((lower urinary tract*[tiab] OR low urinary tract*[tiab]) AND (symptom*[tiab] OR dysfunct*[tiab] OR dys-funct*[tiab] OR diseas*[tiab])) OR LUTS[tiab] OR nocturia[tiab] OR ((urinary[tiab] OR stress[tiab] OR urge*[tiab] OR giggle[tiab]) AND incontinence[tiab]) OR enure*[tiab] OR urinary tract infect*[tiab] OR cystitis[tiab] OR ((dysfunct*[tiab] OR dys-funct*[tiab]) AND (voiding[tiab] OR bladder[tiab])) OR dyscoordinated voiding[tiab] OR voiding dyscoordination[tiab] OR ((urinary[tiab] OR overactiv*[tiab] OR hypoactiv*[tiab]) AND bladder[tiab]) OR bedwett*[tiab] OR ((bed[tiab] OR diurna*[tiab] OR daytime[tiab] OR day time[tiab] OR nocturnal[tiab] OR nighttime[tiab] OR nightime[tiab] OR night time[tiab]) AND wett*[tiab]) OR voiding mechanic*[tiab] OR pollakiuria[tiab] OR oliguria[tiab] OR stranguria[tiab] OR dysuria[tiab] OR ((urine[tiab] OR urinary[tiab] OR void*[tiab] OR mict*[tiab]) AND ("weak stream"[tiab] OR straining[tiab] OR large capacity[tiab] OR holding[tiab] OR retention[tiab] OR frequent[tiab])) OR (post-mict*[tiab] AND dribble*[tiab]) OR (post-void*[tiab] AND residual urine[tiab]))

AND

("Child"[Mesh] OR "Adolescent"[Mesh] OR child*[tiab] OR adolescen*[tiab] OR pediatr*[tiab] OR paediatr*[tiab] OR teen*[tiab] OR youth[tiab] OR kids[tiab] OR boy*[tiab] OR girl*[tiab])

Embase

('constipation'/exp OR constipat*:ab,ti OR obstipat*:ab,ti OR 'bladder and bowel dysfunction*':ab,ti OR 'dysfunctional elimination syndrome*':ab,ti OR encopres*:ab,ti OR ((faecal:ab,ti OR fecal:ab,ti OR rectal:ab,ti OR rectum:ab,ti OR imcomplet*:ab,ti OR incomplet*:ab,ti) AND (impact*:ab,ti OR evacuat*:ab,ti)) OR defecat*:ab,ti OR defaecat*:ab,ti OR stool*:ab,ti OR ((bowel:ab,ti OR abdom*:ab,ti) AND (function*:ab,ti OR habit*:ab,ti OR movement*:ab,ti OR symptom*:ab,ti OR motion*:ab,ti)))

AND

('lower urinary tract symptoms'/exp OR 'enuresis'/exp OR 'urine incontinence'/exp OR 'micturition'/exp OR 'bladder'/exp OR 'bladder function'/exp OR 'oliguria'/exp OR 'urine retention'/exp OR (('lower urinary tract*':ab,ti OR 'low urinary tract*':ab,ti) AND (symptom*:ab,ti OR dysfunct*:ab,ti OR 'dys-funct*':ab,ti OR diseas*:ab,ti)) OR LUTS:ab,ti OR nocturia:ab,ti OR ((urinary:ab,ti OR stress:ab,ti OR urge*:ab,ti OR giggle:ab,ti) AND incontinence:ab,ti) OR enure*:ab,ti OR 'urinary tract infect*':ab,ti OR cystitis:ab,ti OR ((dysfunct*:ab,ti OR 'dys-funct*':ab,ti) AND (voiding:ab,ti OR bladder:ab,ti)) OR 'dyscoordinated voiding':ab,ti OR 'voiding dyscoordination':ab,ti OR ((urinary:ab,ti OR overactiv*:ab,ti OR hypoactiv*:ab,ti) AND bladder:ab,ti) OR bedwett*:ab,ti OR ((bed:ab,ti OR diurna*:ab,ti OR daytime:ab,ti OR day time:ab,ti OR nocturnal:ab,ti OR nighttime:ab,ti OR nightime:ab,ti OR 'night time':ab,ti) AND wett*:ab,ti) OR 'voiding mechanic*':ab,ti OR pollakiuria:ab,ti OR oliguria:ab,ti OR stranguria:ab,ti OR dysuria:ab,ti OR ((urine:ab,ti OR urinary:ab,ti OR void*:ab,ti OR mict*:ab,ti) AND ('weak stream':ab,ti OR straining:ab,ti OR 'large capacity':ab,ti OR holding:ab,ti OR retention:ab,ti OR frequent:ab,ti)) OR ('post-mict*':ab,ti AND dribble*:ab,ti) OR ('post-void*':ab,ti AND 'residual urine':ab,ti))
AND
('child'/exp OR 'adolescent'/exp OR child*:ab,ti OR adolescen*:ab,ti OR pediatr*:ab,ti OR paediatr*:ab,ti OR teen*:ab,ti OR youth:ab,ti OR kids:ab,ti OR boy*:ab,ti OR girl*:ab,ti)
NOT ('conference abstract'/it OR 'conference paper'/it)
AND ([child]/lim OR [preschool]/lim OR [school]/lim OR [adolescent]/lim)

PsycINFO

(DE "Constipation" OR TI (constipat* OR obstipat* OR "bladder and bowel dysfunction*" OR "dysfunctional elimination syndrome*" OR encopres* OR ((faecal OR fecal OR rectal OR rectum OR imcomplet* OR incomplet*) AND (impact* OR evacuat*)) OR defecat* OR defaecat* OR stool* OR ((bowel OR abdom*) AND (function* OR habit* OR movement* OR symptom* OR motion*))) OR AB (constipat* OR obstipat* OR "bladder and bowel dysfunction*" OR "dysfunctional elimination syndrome*" OR encopres* OR ((faecal OR fecal OR rectal OR rectum OR imcomplet* OR incomplet*) AND (impact* OR evacuat*)) OR defecat* OR defaecat* OR stool* OR ((bowel OR abdom*) AND (function* OR habit* OR movement* OR symptom* OR motion*))))
AND
(DE "Urinary Incontinence" OR DE "Urination" OR DE "Bladder" OR DE "Urinary Function Disorders" OR TI ((("lower urinary tract*" OR "low urinary tract*") AND (symptom* OR dysfunct* OR "dys-funct*" OR diseas*)) OR LUTS OR nocturia OR ((urinary OR stress OR urge* OR giggle) AND incontinence) OR enure* OR urinary tract infect* OR cystitis OR ((dysfunct* OR "dys-funct*") AND (voiding OR bladder)) OR "dyscoordinated voiding" OR "voiding dyscoordination" OR ((urinary OR overactiv* OR hypoactiv*) AND bladder) OR

bedwett* OR ((bed OR diurna* OR daytime OR day time OR nocturnal OR nighttime OR nightime OR night time) AND wett*) OR "voiding mechanic*" OR pollakiuria OR oliguria OR stranguria OR dysuria OR ((urine OR urinary OR void* OR mict*) AND ("weak stream" OR straining OR "large capacity" OR holding OR retention OR frequent)) OR ("post-mict*" AND dribble*) OR ("post-void*" AND "residual urine")) OR AB (((("lower urinary tract*" OR "low urinary tract*") AND (symptom* OR dysfunct* OR "dys-funct*" OR diseas*)) OR LUTS OR nocturia OR ((urinary OR stress OR urge* OR giggle) AND incontinence) OR enure* OR urinary tract infect* OR cystitis OR ((dysfunct* OR "dys-funct*") AND (voiding OR bladder)) OR "dyscoordinated voiding" OR "voiding dyscoordination" OR ((urinary OR overactiv* OR hypoactiv*) AND bladder) OR bedwett* OR ((bed OR diurna* OR daytime OR day time OR nocturnal OR nighttime OR nightime OR night time) AND wett*) OR "voiding mechanic*" OR pollakiuria OR oliguria OR stranguria OR dysuria OR ((urine OR urinary OR void* OR mict*) AND ("weak stream" OR straining OR "large capacity" OR holding OR retention OR frequent)) OR ("post-mict*" AND dribble*) OR ("post-void*" AND "residual urine")))
AND
(AG (childhood OR adolescence) OR DE "Offspring" OR TI (child* OR adolescen* OR pediatr* OR paediatr* OR teen* OR youth OR kids OR boy* OR girl*) OR AB (child* OR adolescen* OR pediatr* OR paediatr* OR teen* OR youth OR kids OR boy* OR girl*))

Cochrane library

(constipat* OR obstipat* OR "bladder and bowel dysfunction*" OR "dysfunctional elimination syndrome*" OR encopres* OR ((faecal OR fecal OR rectal OR rectum OR imcomplet* OR incomplet*) AND (impact* OR evacuat*)) OR defecat* OR defaecat* OR stool* OR ((bowel OR abdom*) AND (function* OR habit* OR movement* OR symptom* OR motion*)))
AND
((("lower urinary tract*" OR "low urinary tract*") AND (symptom* OR dysfunct* OR "dys-funct*" OR diseas*)) OR LUTS OR nocturia OR ((urinary OR stress OR urge* OR giggle) AND incontinence) OR enure* OR "urinary tract infect*" OR cystitis OR ((dysfunct* OR "dys-funct*") AND (voiding OR bladder)) OR "dyscoordinated voiding" OR "voiding dyscoordination" OR ((urinary OR overactiv* OR hypoactiv*) AND bladder) OR bedwett* OR ((bed OR diurna* OR daytime OR "day time" OR nocturnal OR nighttime OR nightime OR "night time") AND wett*) OR "voiding mechanic*" OR pollakiuria OR oliguria OR stranguria OR dysuria OR ((urine OR urinary OR void* OR mict*) AND ("weak stream" OR straining OR "large capacity" OR holding OR retention OR frequent)) OR ("post-mict*" AND dribble*) OR ("post-void*" AND "residual urine"))
AND
(child* OR adolescen* OR pediatr* OR paediatr* OR teen* OR youth OR kids OR boy* OR girl*)

Supplemental Content 2

Explanation of Prevalence Critical Appraisal

Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. (2015) Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015; 13:147–153.

Detailed interpretation for this systematic review

Answers: Yes, No, or Unclear

1. Was the sample frame appropriate to address the target population?

Score yes if all answers were yes: boys and girls were included; age range was between 4 to 17 years (inclusive); there were no inappropriate inclusions or exclusions for example exclusion because of behavioral problems.

2. Were study participants recruited in an appropriate way?

Score yes if: the study invited an appropriate random sample or all patients from a community i.e. multiple schools or the study included consecutive or random sample or all of patients from a clinic.

3. Was the sample size adequate?

Variables used to define the sample size: Z=1.96; P= (proportion calculated in the included article); d=0.05 unless P < 10% or P >90% then d = 0.5P.

4. Were the study subjects and setting described in detail?

Score yes if all answers were yes: description of boy/girl ratio; description of age characteristics; description of number of children with functional constipation; description of the setting; description of geographic region of the study or name of the hospital; in/exclusion criteria described.

5. Was data analysis conducted with sufficient coverage of the identified sample?

Score yes if: there was a 100% response rate or if there were no differences in characteristics between responders/non-responders, inclusions/refusers i.e. boy/girl ratio, mean age.

6. Were valid methods used for the identification of the condition?

The question was separately answered for the condition LUTS and UTI.

Score yes if: there was an appropriate definition reported of the LUTS, which means definitions according the ICCS terminology document,[1] for UTI this means a diagnosis by

urinalysis and culture.

7. Was the condition measured in a standard, reliable way for all participants?
The question was separately answered for the condition LUTS and UTI.
Score yes if: the same questionnaire or instrument was used for all patients. In the case when LUTS was based on the diagnosis of the physician. There was one physician that made all the diagnosis or if there were more physicians making the diagnosis, there were no differences in experience between the physicians.

8. Was there appropriate statistical analysis?
The question was separately answered for the condition LUTS and UTI.
Score yes if: the authors reported the percentage of children with LUTS or UTI in children with functional constipation or the authors reported the numerator and denominator i.e. number of patients with LUTS or UTI and functional constipation and the total number of patients with functional constipation.

9. Was the response rate adequate, and if not, was the low response rate managed appropriately?
Score yes if: the response rate was above 70%2 or when the response rate was between 50% and 70% (modest response rate), the reasons for non-response appear to be unrelated to the LUTS or UTI and the non-responders were comparable with the responders?[2]

References

1. Austin PF, Bauer SB, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: Update report from the standardization committee of the international children's continence society. Neurourol Urodyn. 2016;35(4):471-481.
2. Gordon N. A question of response rate. Science. 2002;25(1):25.

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Comunity population								
Chung (2010) Republic of Korea	Cross-sectional n(Total): 16516 n(FC): 8219	? (5-13) B:8260 G: 8256	Earlier treatment for bladder or bowel dysfunction	**≥1 criterion** *Frequency < 3 p/w, *BSS type 1 or 2, *FI, *Difficult or painful defecation Questionnaire	DVS score Including NE, Frequency, Urgency, UI, Holding maneuver or postpone voiding Questionnaire	/	Invitation of parents in 26 Kindergarten and 27 elementary school	October-December 2006
Esezobor (2015) Nigeria	Cross-sectional n(Total): 928 n(FC): 58	10.2 ± 3.5 (5-17) B: 444 G: 484	Not available at the time of visit by the study team	Rome III criteria with the exception of the duration of bowel symptoms criterium Self-developed questionnaire documented by an experienced interviewer	UI ≥ 1x p/w Questionnaire (according to recommendations of the ICCS) documented by an experienced interviewer	/	Invitation of parents in per-urban, largely residential community bordering a public tertiary hospital, in mushin local goverment area of lagos state Nigeria.	6-day period November 2014
Hamed (2017) Egypt	Cross-sectional n(Total): 4652 n(FC): 778	9 ± 2 (6-12) B: 2331 G: 2321		? Questionnaire	EN ? Questoinnaire designed for this study after examining previous studies on monosymptomatic enuresis	/	Invitation of (parents of) primary school children of 12 primary schools in Sohag and Qena Governorates in the South of Egypt	?

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Kajiwara (2004) Japan	Cross-sectional n(Total): 5282 n(FC): 977	9,3 ± 1,7 (7-12) B: 2690 G: 2592	Present or past neurological diseases	Def < 3 p/w Questionnaire (based on International Consultation on Incontinence Questionnaire-Short Form)	DUI >1 p/m in the past 6 months Questionnaire (based on International Consultation on Incontinence Questionnaire-Short Form)	/	Invitation of parents in 11 primary schools (eastern area of Hiroshima city)	Feb-March 2002
Kajiwara (2006) Japan	Cross-sectional n(Total): 202 n(FC): 67	9,3 ± 0,89 (13-15) B: 99 G:103		Def < 3 p/w Questionnaire (based on International Consultation on Incontinence Questionnaire-Short Form)	OAB Frequency >8 x p/d and/or urge incontinence ≥ 1 p/m Questionnaire (based on International Consultation on Incontinence Questionnaire-Short Form)	/	Invitation of students in Junior high school	July-Sep 2001
Kalo (1996) Saudi Arabia	Cross-sectional n(Total): 640 n(FC): 55 n(Encopresis): 25	9,9 ± 2,3 (6-16) B: 320 G: 320		FC and encopresis Questionnaire	UI ≥1 p/m Questionnaire	/	Invitation of parents in primary school	?
Sampaio (2016) Brasil	Cross-sectional n(Total): 829 n(FC): 91	9.1 ± 2.9 (5-17) B: 416 G: 413	Children with neurological problems or who had documented abnormalities of the urinary tract	Rome III criteria Rome III questionnaire for children	Rome III criteria Rome III questionnaire for children	/	Invitation of children from 2 Brazilian cities who happened to pass by the collection points were approached at random	May-July 2015

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Sarici (2016) Turkey	Cross-sectional n(Total): 1984 n(FC): 182	8.92 ± 2.07 (6-13) B: 1018 G: 966		Def < 3 p/w and presence of straining during defecation Questionnaire	En ≥1 p/m Questionnaire	/	Invitation of children from 10 randomly selected primary schools from the two major districts of Ankara.	January-May 2013
Söderstrom (2004) Sweden	Cross-sectional n(Total): 1478 n(FC): 113	First grade (B: 7.4, G:7.3) fourth grade (B+G:10.4) B: 765 G: 713	Incomplete questionnaire	FI (soiling and/or stool incontinence) Questionnaire	DUI ≥1 p/m Questionnaire	/	Invitation of parents in primary school (first and fourth grade)	autumn 1997
Uguralp (2003) Turkey	Cross-sectional n(Total): 1377 n(FC): 171	? (5-9) B: 703 G: 674		**≥1 criterion** *Def <1 p/d, *Painful *Hard *Unusually large * Difficult to pass stool Questionnaire	UI ≥1 p/w Questionnaire	/	Invitation of parents who are willing to participate in elementary schools (with kindergarten or preparatory classes)	?
Primary care								
Loening-Baucke (2007) United States	Review case records n(total): 389 n(FC): 87 (≥ 5 years)	4,9 ± 3,7 (4-17) B: 55 G: 54	Not followed from birth or within the first 6 months of age in a primary care clinic	**≥2 criteria** *Def <3 p/w *Fi ≥1 p/w *Large stools in the rectum or felt on abdominal examination *Passing of stools so large that they obstruct the toilet *Retentive posturing *Painful defecation Diagnosis by physician	DUI, EN, DUI + EN, UI ≥ 1p/w (age of ≥5 years) Diagnosis by physician	/	Medical records	January-June 2004

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Specialist care								
McDonald (2004) Scotland	Review case records n(Total): 34 n(FC): 30	? (2-15) B:G = 2 : 1		Encopresis: passage of normal stool in abnormal places, Constipation: simple constipation and/or overflow soiling Diagnosis by physician	UI ≥ 1x p/w Diagnosis by physician	/	Referred children with soiling stated as main problem in referral letter Medical records	4 month period
Reich (2010) Poland	Cohort n(Total): 126 n(FC): 126	7,5 ± 4,6 (0.13 - 18.3) B: 67 G: 59		Rome III criteria Questionnaire (documented physician)	/	≥ 10^5 bacteria Urine culture	Children admitted to 2nd Department of Pediatrics, Gastroenterology and Nutrition of Wroclaw Medical University (Poland)	January 2006 - December 2008
van Engelenburg van Lonkhuyzen (2016) The Netherlands	RCT n(Total): 53 n(FC): 53	8.8 ± 2.3 (intervention) 8.3 ± 2.3 (control) (5-16) B: 24 G: 29	Prior physiotherapy because of bladder or bowel complaints, urotherapy by another professional at inclusion, endocrine and metabolic disorders, neurological and psychiatric disorders, Down's syndrome, Hirschsprung's disease, >14 points on the total score of the Strengths and Difficulties Questionnaire, drug-induced constipation, prior intestinal surgery (except appendectomy)	Rome III criteria Diagnosis by physician	DUI, EN ? Diagnosis by physician	? ?	Referred children attending regular school	December 2009 - May 2014

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Clavero (1993) Spanje	Review case records n(T): 113 n(FC): 65	9.4 ± ? (4.3 – 14.7) B: 95 G: 18		Secundaire encopresis according DSM III-R criteria Diagnosis by physician	DUI, EN, DUI + EN ? Diagnosis by physician	/	Medical records	?
Dehghani (2013) Iran	Cross-sectional n(Total): 120 n(FC): 120	7.4 ± 3.2 ? B: 47 G: 73	Anatomical causes of constipation, organic cause of constipation, constipation due to another disorder, prior anal surgery, developmental abnormalities, and use of medications that can cause constipation or UTI.	Rome III criteria Questionnaire (documented by researcher)	DUI, EN, Dysuria, dribbling, increased frequency ? Questionnaire (documented by researcher)	Positive urine culture Leukocytes >5-6/ high powerfield Urine analysis and urine culture	Referred children for chronic constipation (≥ 3 months)	?
Foreman (1996) United Kingdom	Review case records n(Total): 63 n(FC): 63	8.4 ± 2.8 ? B: 63 G: 0	Girls (only 2 with encopresis), incomplete data, children with global learning disability	Encopresis according ICD-9 criteria (passage of normal defecation in abnormal places, with or without soiling) Medical record	UI ? Medical record	/	Referred children with encopresis to a psychiatric clinic not corresponding on earlier treatment Medical records	January 1980 – December 1988
Hadjizadeh (2009) Iran	Prospective case-control for FC Case: 85 Control: 280	5.7 ± 2.7 ? B: 25 G: 60 Control Matched on age and gender	Organic cause of the constipation	**≥2 criteria ≥ 2 weeks:** *Infrequent passage of stools *Difficulty passing stools * Feces that are large and hard or in small pieces *Abdominal pain *Palpable stool in the abdomen *Stool in the rectal vault Diagnose by physician	DVS score, EN Questionnaire Modified version of the dysfunctional voiding scoring survey including incontinence, enuresis, dysuria and other urinary symptoms	? Urine analysis and culture	Cases: Referred children for FC Controls: Referred children without FC	April 2004 – March 2005

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Imanzadeh (2013) Iran	Cross-Sectional n(total): 560 n(FC): 480	? (5-15) B: 362 G: 198		**≥1 criterion** *Def <3 p/w *Hard defecation ?	UI ? ?	/	Children with FC or UI	?
Karakelleoglu (1997) Turkey	Prospective case-control for FC Cases: 31 Control: 29	Cases: 5.6 ± ? (2-14) B: 18 G: 13 Controls: 6.8 ± ? (2-14) B: 16 G: 13	Use of medications that can cause constipation, neurogenic constipation, anal anomaly, endocrine disorders, mental retardation	**All criteria** *Def < 3 p/w *Abnormal stools *Very large amount of stools present in the rectal ampulla ?	EN ? ?	Midstream urine:10^5 bacteria /mL Catheter >50x 10^5 bacteria/mL Urine analysis and culture	Cases: Children with chronic FC (≥ 6 months) with or without encopresis Controls: volunteers, def freq between 1 p/2 days and 2 p/d, no gastro-intestinal diseases in history, normal physical examination	?
Kasirga (2006) Turkey	Kasirga (2006) Turkey	Cases: 5.3 ± 4.3 (0.5 – 16) B: 16 G: 22 Controls 6.8 ± 3.9 (0.5 – 15) B: 16 G: 15	Spinal or anal anomaly, endocrine or metabolic disorders	**Both criteria** *Def < 3 p/w *Painful or hard defecation Diagnosis by physician	EN, Urge UI, urgency ? Diagnosis by physician	? Urine analysis and culture	Cases: Children with chronic FC (≥ 6 months) Controls: Children with other than gastrointestinal or urologic symptoms	?

Supplemental Table 1. Characteristics of the included studies

General study information		Population			Condition		Context	
Study + Country of origin	Study design n(Total) n(FC)	Mean age + range in years + n boy, n girl	Exclusion criteria	Definition of FC + Measurement tool	Definition LUTS + Frequency LUTS + Measurement tool	Definition UTI + Measurement Tool	Recruitment	Study Period
Loening-Baucke (1997) United States	Cohort n(Total): 234 n(FC): 234	9 ± 3 (5-18) B: 176 G: 58	Organic disease or intake of medication, Hirschsprung's disease, hypothyroidism, mental deficiency, chronic debilitating diseases, neurologic abnormalities and previous surgery of the colon	All children had stool retention on rectal examination, and 45% had a fecal mass palpable on abdominal examination. Encopresis, defined as fecal incontinence in children with functional constipation, was present in all patients and occurred at least once per week for at least 6 months Diagnosis by physician	DUI, EN, DUI + EN ≥ 1 p/w Diagnosis by physician	Midstream urine: ≥ 50.000 bacteria /mL Catheter ≥10.000 bacteria/mL Urine analysis and culture	Children with chronic FC (≥ 6 months) and FI ≥1 p/w	January 1986 – April 1988 and January 1991 – April 1995
van Dijk (2010) The Netherlands	RCT n(Total): 133 n(FC): 133	6.7 ± 2.3 (4-18) B: 75 G: 58	Received a comprehensive behavioral treatment conducted by a psychologist or psychiatrist in the previous 12 months, used drugs that influence gastrointestinal function other than laxatives and children with organic causes for defecation disorders or other metabolic or renal abnormalities	**≥2 criteria** *Def <3 p/w *Fi ≥ 2 p/w *Passage of large amounts of stool at least once every 7 to 30 days (large enough to obstruct the toilet * Palpable abdominal or rectal fecal mass Questionnaire (documented by researcher)	DUI, EN ? Questionnaire (documented by researcher)	/	Referred children	November 2002 – August 2004

Chapter 7

Summary and general discussion

Summary and general discussion

The main objective of this thesis was to investigate whether adding physiotherapy to conventional treatment is an effective and cost-effective treatment strategy for children, aged 4-17 years, with functional constipation (FC) in primary care. Therefore, we have performed the BOKi pragmatic randomized controlled trial (in Dutch "Behandeling van Obstipatie bij KInderen").

In this chapter we summarize the main findings of the BOKi trial and the associated studies. Furthermore, we explain the methodological considerations of the BOKi trial. Then, we discuss the clinical implications of our findings for the management of children with FC in primary care, the recommendations for the management of children with FC and the implications for the clinical guidelines. Finally, we provide suggestions for future research.

Main findings

Effectiveness and cost-effectiveness of physiotherapy for childhood FC in primary care

FC in children has a multifactorial etiology: stool withholding behavior, pelvic floor dyssynergia, toilet training, contextual factors (school change, bullying, family problems) all may play a role. It is hypothesized that chronicity of FC can be prevented if treatment starts early in the process and that physiotherapy with a focus on the pelvic floor dyssynergia along with a focus on the inherent multifactorial etiology of FC might contribute to the resolution of the symptoms, more so than care as usual. Physiotherapy has shown promising results in hospital settings, but evidence for the effectiveness in primary care is lacking. Therefore, we have formulated the following research question: "Is adding physiotherapy to the conventional treatment for childhood FC in primary care a more effective treatment strategy than conventional treatment alone?". To answer this question, we designed and conducted a pragmatic randomized controlled trial with a follow-up period of eight months **(Chapter 2)**. As the primary outcome measure we chose treatment success defined as "absence of FC symptoms and no laxative use". Secondary outcome measures were treatment success defined as "absence of FC symptoms irrespective of laxative use", quality of life and global perceived treatment effect. In total, 134 children aged 4-17 years and diagnosed with FC by a general practitioner (GP) or pediatrician were randomized to one of the two interventions: physiotherapy added to usual care treatment (physiotherapy group, n=67) and conventional treatment alone (CT group, n=67).

In **Chapter 3** we describe the results of the BOKI trial: over eight months, physiotherapy added to conventional treatment was not superior to conventional treatment alone in terms

of the two definitions of treatment success: "absence of FC and no laxative use" (adjusted Relative Risk, aRR 0.80; 95% CI 0.44 to 1.30), "absence of FC irrespective of laxative use" (aRR 1.12; 95% CI 0.85 to 1.34), and quality of life. In contrast to these findings, parents of the children in the physiotherapy group reported significantly more symptom improvement compared to parents in the CT group. In a predefined subgroup analysis of the findings in children with chronic symptoms (n=72), with symptom chronicity defined as continuous or regular laxative use (≥3 periods) in the 12 months before inclusion, a statistically significant difference between the physiotherapy and CT group was found on the secondary outcome treatment success defined as "absence of FC irrespective of laxative use" (aRR 1.40; 95% CI 1.00 to 1.63). The other outcomes, treatment success defined as "absence of symptoms and no laxative use", quality of life and global perceived treatment effect did not show statistically significant differences between interventions in the subgroup of children with chronic symptoms. Our conclusion from these results is that adding physiotherapy to conventional care is not an effective treatment strategy for all children with FC in primary care. Our subgroup analysis suggests that physiotherapy might be effective for children with chronic symptoms, but this needs to be further evaluated in a larger trial.

Alongside the randomized controlled trial we have performed a cost-effectiveness analysis from a societal perspective **(Chapter 4)**. Although Chapter 3 showed that the difference in treatment success rates between the two groups was small and not significant for all children in primary care, a cost-effectiveness analysis is valuable because the cost-effectiveness evaluation is about the balance between costs and effects, and differences in costs might exist between treatment groups. The mean societal costs per child in the physiotherapy group were €155 euros (95%CI €-12 to € 310) higher compared to the mean societal costs in the CT group. The incremental cost effectiveness ratios (ICER) to treat one additional child successfully were €24 060 (95%CI €-16 275 to €31 390)) for the outcome treatment success defined as "absence of FC symptoms and no laxative use", and €1 221 (95%CI €-12 905 to 10 956) for treatment success defined as "absence of FC symptoms irrespective of laxative use". There is no explicit cost-effectiveness threshold available for both outcome measures, which hampers the ability to draw firm conclusions regarding the cost-effectiveness of physiotherapy added to CT compared to CT alone. However, regardless of the amount society would be willing to pay, the probability that physiotherapy added to CT will be more cost-effective compared to CT alone will not exceed 0.5 according to the first definition of treatment success and 0.9 according to the second definition. Therefore, we conclude that adding physiotherapy to CT in all children with FC in primary care cannot be considered cost-effective. For the subgroup of children with chronic symptoms, the corresponding ICERs to treat one additional child successfully were more positive, respectively €2 134 (95%CI €-24 975 to 17 192) and €571 (95%CI €11 to 3 566). However, the results of the

cost effectiveness acceptability curves (CEAC), that are based on the uncertainty in cost and effect differences, are less obvious. Therefore, further evaluation in the subgroup population of children with chronic symptoms is needed.

Parent-child agreement on quality of life

Quality of life is an important measure to determine the impact of a disease on the wellbeing of a patient. This measure is not only used in research but also forms a part of daily practice of clinicians. Measuring quality of life in children is complicated because there is substantial debate regarding the most appropriate respondent for assessing a child's quality of life: the child itself or the parent(s). In **Chapter 5** we have used the baseline characteristics collected in the BOKi trial to evaluate the parent-child agreement on the quality of life of children aged 8-17 years. Quality of life of the child was assessed with a child self-report and a parent-proxy report version of the Defecation Disorder List, a disease-specific quality of life questionnaire, and the EuroQol-5-dimension-Youth Visual Analogue Scale, a questionnaire to measure the general health status of the child. We demonstrated that on a group level the parent-child agreement on quality of life, both the disease-specific quality of life as the general health status, is good. This indicates that both a parent report and a child-self report can be used in research to examine the quality of life of children with FC. However, a substantial number of parent-child pairs differed considerably on their rating of the quality of life of the child. Age and gender were not associated with the level of parent-child agreement. Therefore, we recommend clinicians to ask both the child and the parent(s) to get an impression of the impact of the FC on the quality of life of the child.

Bladder-bowel dysfunction

Bladder and bowel problems in children often occur together according to the literature, but the actual extent of the problem in children with FC is unknown. In a systematic review of the literature **(Chapter 6)**, we included 23 studies reporting on the prevalence of bladder symptoms in children with FC. Twenty-two studies (12,281 children with FC) reported on lower urinary tract symptoms (LUTS) and seven studies (687 children with FC) on urinary tract infections (UTI). The prevalence of LUTS (defined as a summary measure of symptoms) in children with FC varied between 37% and 64% (3 studies). The prevalence of single bladder symptoms ranged from 2% for the symptom "straining" to a maximum of 47% for the symptom "nighttime urinary incontinence". Urinary tract infections (UTI) were reported in 6% to 53% of the children with FC. There was much heterogeneity in the definitions of bladder symptoms and FC and therefore we decided it was not meaningful to generate pooled estimates on the prevalence of bladder symptoms in children with FC.

In 12 of the 23 studies bladder symptoms were identified in children with and without FC,

which allows us to compare the prevalence rates. Two of these 12 studies reported on the prevalence of LUTS (defined as a summary measure of symptoms), and the results showed that children with FC had significantly more LUTS compared to children without FC, the RRs were 4.54 (95%CI 3.08-6.71) and 6.35 (95%CI 4.32-6.71). Ten other studies compared the prevalence of one or more single bladder symptoms between children with and without FC (in total 18 comparisons were made). In 12 comparisons (67%) the relative risks showed that children with FC had significantly more often bladder symptoms compared to children without FC. Based on these results we concluded that children with FC were more likely to have bladder symptoms compared to children without FC. The two studies comparing the proportion of UTIs in children with and without FC did not find statistically significant differences between groups, but the sample sizes of these studies were rather small. Because of the high prevalence of bladder symptoms in children with FC, we recommend GPs and pediatricians to actively ask about bladder symptoms in children with FC.

Methodological considerations

Pragmatic randomized controlled trial

We have chosen to design a pragmatic randomized controlled trial (RCT) to investigate whether adding physiotherapy to the current best treatment option is a better treatment strategy compared to the current best treatment option alone for children with FC in primary care.[1] Our purpose was to investigate the (cost-)effectiveness of the treatment — that is, the benefit and costs of adding physiotherapy to conventional treatment, in real-world clinical practice. Information regarding the effectiveness and cost-effectiveness is necessary to decide which treatment strategy should be recommended in daily practice.[1,2] The decision to design a pragmatic RCT instead of a more explanatory RCT has consequences for the applicability of the results of the RCT.[1]

The BOKi trial was undertaken in the clinical setting of the Dutch general practice. Children were recruited in 93 general practices (209 GPs) and five general pediatric outpatient departments in district hospitals. We recruited children with a diagnosis of FC as considered by their GP. This means that the included children not necessarily fulfill the Rome criteria for FC at baseline. We refrained from too strict selection criteria so that the participants were a representative reflection of those seen in GP practices. In addition, children were allowed to use laxatives at baseline, this reflects the daily practice in which physiotherapy is an addition to the conventional treatment. As a consequence, FC related symptoms of these children might have been reduced at baseline. In total, 100 out of the 134 (75%) included children did fulfill the Rome III criteria for FC, and 25 out of the 34 (74%) children that did not fulfill Rome III criteria did use laxatives at baseline. This means that only nine of the 134 children (5%) that were diagnosed with FC by their GP or pediatrician, did not fulfill Rome III criteria or

used laxatives at baseline. These children were equally distributed between the intervention and control group. The duration of symptoms of children in the trial was somewhat higher in comparison to those who refused to participate in the trial (Chapter 2). Considering all this, we believe that the children in our study did not differ much from children in studies using Rome criteria as a strict inclusion criteria. But as compared with daily general practice, children with chronic symptoms may be overrepresented in the trial.

Once a child was allocated to a treatment group, the child's own GP, and in the intervention group also a physiotherapist with additional education in the treatment of children with bladder and bowel problems, were designated to provide their usual treatment. Children did not necessarily receive the exact same treatment regimen as the treatments, both the physiotherapy and the conventional treatment, were tailored to the patient's needs. In addition, children were not followed closely to ensure treatment adherence. Therefore, flexibility in the delivery of the treatment and adherence to the treatment was in line with daily clinical practice. GPs, parents and children were aware of their treatment allocation, as is usually the case in real-world clinical practice. These deliberate choices made us incorporate the variations seen between patients. The participants thus reflect those seen in clinical practice to whom the treatments will be applied. Therewith we are convinced we generated high external validity.

A well-known downside of the choice to not blind the children, parents, and healthcare professionals for treatment allocation is the potential for response bias in the outcome measures. Response bias hampers internal validity. Our primary outcome "treatment success" is less sensitive for response bias compared to the secondary outcomes "global perceived treatment success" as noted by the parents and quality of life. When interpreting our results one should be aware that the results reflect the (cost-)effectiveness of adding physiotherapy to conventional treatment in real-world clinical practice, it is not an etiologic study. Inherent to a pragmatic RCT design, conclusions on the efficacy of physiotherapy and the effects of the treatment conducted under ideal conditions, must be drawn with caution.

Definition of the outcome measure treatment success

Our primary outcome was treatment success defined as the absence of FC according to the Rome-III criteria and no laxative use. Thus, a successfully treated child was required to fulfill none or only one of the six Rome-III criteria and should not use laxatives anymore. One may argue that this is not a realistic goal for the short and mid-term follow up, given the assumption that FC is a chronic disease. In chronic diseases treatment should be directed to the reduction of bothersome symptoms and the improvement of the quality of life. Therefore, aiming for full recovery of the disease as we implicitly did when choosing

our primary treatment outcome might not be possible, making this primary outcome less relevant according to the patients perspective. Our secondary outcome: treatment success defined as "the absence of FC according to the Rome-III criteria irrespective of laxative use", might be more relevant. Previous research showed that there is great variety in the definition of treatment success used in studies evaluating treatments for childhood FC, and there is an ongoing debate on how to define treatment success.[3,4]

The definition of treatment success influences the conclusions about the (cost-)effectiveness of the intervention: the difference in treatment success percentages between intervention and control group was larger for the secondary outcome than for the primary outcome, but not statistically significant. This means that children in the physiotherapy group more often reported to be free of FC symptoms after eight months, but also more often reported using laxatives. Previous studies showed that there is a discrepancy between clinical care recommendations on defining success and parents' experiences and expectations when caring for a child with FC.[5,6] More research is needed to examine what children and parents would define as successful treatment, what they consider as a realistic investment in time and efforts to reach a desired outcome, and if the investment in time and efforts will depend on the outcome. In our study, parents in the physiotherapy group reported statistically significant more global perceived effect of the treatment compared to parents in the control group, but we did not investigate whether children and parents would consider this as an improvement that was worth the investment. Especially in children with chronic symptoms it would be interesting to evaluate whether children and parents consider a treatment is worth the efforts when the outcome will be that the FC symptoms are absent or even only reduced, but medications are still necessary.

Duration of follow-up

We hypothesized that physiotherapy might be more effective compared to conventional treatment alone because physiotherapy included rehabilitation of the pelvic floor muscles in combination with a patient tailored education to tackle other factors that might be involved in the origin and persistence of FC. Physiotherapy is therefore aimed to contribute to long lasting lifestyle and behavioral changes that are important for the prevention of recurring symptoms. From that perspective our follow-up of eight months might have been too short to assess the maximum effect of physiotherapy treatment. A longer follow-up period of 24 months would therefore be more ideal, but was not possible due to limited financial resources.

Measuring quality of life and cost-utility analysis in children

Measuring the quality of life in children is challenging because there is a debate who is

the most appropriate respondent to assess a child's quality of life: the parent or the child (Chapter 5).[7] In this study we have used two questionnaires to measure the child's quality of life and both questionnaires were completed by the parent, as well as by the child when aged eight years onwards (child report). A disease-specific quality of life questionnaire: the defecation disorder list was used, because a disease-specific questionnaire is more sensitive to identify effects of treatments on symptoms of FC.[8,9] In addition, we have chosen for the EQ5D-Y-3L because it was expected that with this generic quality of life questionnaire we could calculate utilities for the pre-planned cost-utility analysis.[10]

Cost-utility analyses are used to calculate the extra costs to gain one additional quality-adjusted life year (QALY).[11] Cost-utility analyses based on QALYs are necessary to compare the balance between costs and effects for different treatments for different diseases.[11] At the start of our study a research group was working to determine child tariffs to calculate utilities with the EQ-5D-Y questionnaire, which are needed to calculate QALY's. The utility scores are based on five questions related to: mobility, looking after oneself, doing usual activities, having pain or discomfort, feeling worried, sad or unhappy.[12] The child tariffs were expected to be available at the end of the trial, but this was not the case. As such, we decided to use the adult tariffs as a proxy for the child tariffs.[12] The results of the cost-utility analysis with adult tariffs showed that a substantial part of the utility scores were below zero, indicating that the parents assessed the quality of life of the child as worse than death. This was not in line with the last question of the EQ-5D-Y questionnaire, on which parents were asked to score the today's health of the child on a scale of 0 to 100, and reported an average health status of 85 for their child (Chapter 3 & 5). Therefore, we considered the results of the cost-utility analysis as not reliable and the results were not reported.[12] It is not surprising that utility scores were not transferable between adults and children, as it is normal for a young child that he/she needs help with self-care activities like washing, while this is very debilitating for adults.[12] More research, investigating child tariffs to calculate utility scores for children is needed before reliable cost-utility analyses can be performed in a childhood population.

Management of children with FC in primary care

Childhood FC is a common problem with a great impact on the child and family, but often difficult to manage.[13,14] In the Netherlands, the GP is usually the first healthcare professional to be consulted by a child (and the parents) with FC symptoms, but the child is often living with symptoms for months or years before the GP is consulted.[5,15] Currently the management of children with FC in primary care is directed to resolving FC related symptoms, and includes education, dietary advice, toilet training, and the prescription of laxatives.[14,16,17] This approach does justice to the multifactorial etiology of FC and is in line with studies that showed that

parental education is a mainstay of the treatment for children with FC.[5] However, providing comprehensive education can be time-consuming and be limited by system constraints such as the time that is available for a consultation.[5,15] Previous studies showed that there is often a disconnect between clinical care recommendations and parents' experiences caring for a child with FC.[5,18] Important aspects of which GPs needs to be aware of in the management of children with FC are discussed below.

FC has a multifactorial etiology

FC is a problem with a multifactorial etiology. Toilet training, stool withholding behavior, lifestyle factors, pelvic floor dysfunction, familiar or genetic predisposition, changes in the child's environment (new school, bullying, the birth of a sibling, parents with problems) may all play a role.[13] The standard approach with education, toilet training, non-medical advices and the prescription of laxatives is not for all children a successful approach to reduce the bothersome symptoms.[19,20] A recent network meta-analysis, in which our BOKi trial was included, showed that for children with chronic constipation the standard medical care approach is a better treatment strategy than a non-pharmacologic treatment approach alone.[21] However, any additional non-pharmacological treatment could increase benefits for children with chronic constipation because it potentially addresses more aspects of the condition, and physiotherapy was the most beneficial non-pharmacologic treatment option.[21] Therefore, physiotherapy is a useful addition when standard medical treatment is not successful for a child with chronic constipation.[21,22]

FC tends to become chronic

In many children with FC the symptoms become chronic.[19,20] This observation was also highlighted in the BOKi trial, with 103 children (79%) recruited as a prevalent case (meaning the child has had at least one consultation for FC in the 12 months before enrollment and was still having symptoms at inclusion). Among those prevalent cases the parents reported symptom chronicity in 67 children (65%), while many of those children with chronic symptoms have consulted the GP only once for the FC.

This indicates that more attention to the potential chronic nature of FC is required, even if it is a first episode. We noticed that children (and/or the parents) considered the FC as resolved when the child has had some normal bowel movements. Therefore, even when the clinician had recommended to use the laxatives for a longer period, many children (and/or the parents) decided to stop using laxatives in that situation. This strengthens the importance of closely follow-up children with FC. Clinical guidelines, advise to use laxatives for at least two months, and if FC symptoms are resolved after two months, the laxatives can be tapered off with active monitoring of the symptoms.[14,16,17] It is important that children (if

age appropriate) and parents are instructed to monitor symptoms, i.e. to identify (persistent) symptoms and to be alert for recurring symptoms because it is known that children do often underestimate FC related symptoms.[15,23] This monitoring may need supervision by the GP to avoid suboptimal treatment and to prevent the treatment from being continued too short.[5,18] As we cannot predict which children are at high risk to develop chronic constipation, we recommend active monitoring of symptoms and treatment adherence by the GP for all children with FC.[24]

Co-occurrence of bladder and bowel problems

Children with FC are more likely to develop bladder problems, for example daytime or nighttime urinary incontinence, overactive bladder, urgency, and decreased or increased frequency of micturition (Chapter 6). The underlying pathophysiology of the co-occurrence of bladder and bowel problems is not completely understood, but two main pathways are assumed. First, there may be a mechanical problem, originated by the close proximity of the bladder and bowel.[25,26] Second, there may be a neurogenic problem, originated by the shared embryologic origin of the genito-urinary tract and gastro-intestinal system in the hindgut.[27,28] Therefore, GPs and other health care professionals need to be alert for concomitant bladder problems in children presenting with FC. But also vice versa: awareness of FC in children presenting with bladder symptoms is necessary.

In summary

The management approach for FC described in the clinical guidelines is in line with what we would recommend, but in practice this does not always emerge. GPs still too often see constipation as a symptomatic condition rather than a chronic problem.[5] It is also important for GPs to be aware of potential bladder problems that often co-occur with FC. Below we have summarized the recommendations to improve the management of children with FC in primary care.

Recommendations for the management of childhood FC in primary care

As argued above, children with FC will benefit from prompt and thorough treatment. Counselling of the children and parents and active monitoring of symptoms and treatment adherence is crucial in the management of children with FC.[5] As we cannot predict which children are at high-risk for developing chronic symptoms,[24] we recommend the following for the management of children, aged 4 to 17 years, with FC in primary care.

Start with standard medical treatment that includes education, toilet training, dietary advice and prescription of laxatives. Education and counselling of children (if age appropriate) and the parents is a crucial part of the treatment and is frequently insufficiently addressed.[5,18]

Education needs to focus on 1) the potential chronic character of FC, 2) the vicious circle in which many children end up in which painful defecation leads to stool withholding behavior that results in large stools and more painful defecation etc., and 3) the role the parents might play, for example by encouraging children to hurry when using the toilet. In addition, the multifactorial etiology that might play a role in the onset and maintenance of the symptoms needs to be examined and openly discussed, including physical, psychological, behavioral and social aspects. Toilet training needs to be explained, just as the adequate intake of fluids and fibers. Finally, laxatives are often necessary to break the vicious circle of pain, stool withholding and large stools.

In addition, GPs may advise parents and adolescents to visit the website "thuisarts.nl" of the Dutch Society of GPs.[29] On this website one can find general information about constipation, and two instructional videos: one focusing on normal bowel movements and symptoms that are related to constipation and the other one focuses on toilet training for children.

Secondly active monitoring of the child with FC is warranted. The complexity of childhood FC is often underestimated, and one consultation during which education, toilet training and dietary advice is given, and laxatives are prescribed is mostly insufficient to achieve treatment success.[5,18] GPs need to check after a couple of weeks in a (telephone) consultation whether parents and children (if age appropriate) did understand the instructions to identify persistent or recurring symptoms correctly.[18] In addition, the adherence to and effects of the laxatives needs to be discussed.[30] Through active monitoring of symptoms, children can be prevented from suboptimal or delayed treatment.

If standard medical care will not lead to improvement of symptoms and in case of more complex problems, getting help from a physiotherapist specialized in childhood bladder and bowel problems should be considered.[21,22] In the Netherlands this type of therapy is easily accessible, with and without referral by the GP. The treatment needs motivation form child and parents, because exercises at home are part of the treatment.

Referral to a pediatrician for FC or to (in Dutch) "poep-poli's" is rarely indicated. Only when a GP is in doubt as to whether the constipation has an organic or metabolic cause referral is indicated.[17] After exclusion of organic or metabolic pathology by the pediatrician, the next step of pediatricians is to reassess the dosage of the laxative treatment or to refer the child to a specialist physiotherapist or an urotherapist. Urotherapists are specialist nurses in the treatment of childhood bladder and bowel problems with competencies quite similar to specialist physiotherapists. Both reassessing the dosage of laxatives and referral to specialist physiotherapists can also be implemented in primary care.

Implications for clinical guidelines

The BOKI trial and the related studies are consistent with the view that FC in children has a significant impact on the child and family and often becomes chronic. Early and long-term treatment and monitoring is recommended, with the expectation that this will prevent a chronic course. To achieve this, it is important that the various professionals involved in the care of children with constipation reach agreement on the recommendations in their guidelines. It is also important that they discuss the division and coordination of tasks in order to optimize the management of FC.

These professionals are general practitioners, pediatricians, public health pediatricians (in Dutch jeugdartsen), and specialist physiotherapists and the following three guidelines are used by these professionals:
a) The NHG guideline "Constipation" (2010) deals with constipation in children as well as in adults in general practice.16
b) The Multidisciplinary Guideline (MDR) provides recommendations for the diagnosis and treatment of "Constipation in children aged 0 to 18 years" and was written on the initiative of the Dutch Association for Pediatricians and the NHG (2009, update 2015).[17]
c) The Guideline “Toilet training for urine and feces” is issued by the Dutch Center for Youth and Health Care (2011) for use by public health pediatricians. With regard to defecation problems, the emphasis in this guideline is on toilet training, both for urine and feces, and therefore contains questions about fecal incontinence, which can be a consequence of constipation. The public health pediatricians also participated in the development of the above mentioned MDR.[31]
Physiotherapists who are specialists in the treatment of children with FC do have a master in pediatric physiotherapy or pelvic physiotherapy and have additional education in childhood bladder and bowel problems. Their umbrella organization, the Royal Dutch Society for Physiotherapy (KNGF), has contributed to the MDR, as well as the Dutch Center for Youth and Health Care.

Guideline “Constipation” for general practitioners

The guideline for GPs dates from 2010. At the next revision it is advisable to consider clearly separating the recommendations for children and adults or making separate guidelines. In children, the focus should be on managing FC as this is by far the most common type of constipation in this age group.[13] In adults with constipation, there is a much higher risk of somatic pathology.[13] That does not mean that the management of adults with FC is very different from that in children. However, children need an age-appropriate approach with attention to psychosocial factors, pelvic floor rehabilitation tailored to children and involving parents in the treatment.[13] Besides, more emphasis in a revised guideline could be given to

the prevention of chronicity, which may need monitoring of symptoms for long periods of time, increasing of treatment adherence to laxatives and more attention on toilet training exercises.

In summary: revised GP guidelines should provide recommendations to the following questions:

- How to identify the problem in time?
- How to make an adequate diagnosis and initiate appropriate treatment?
- When to refer to specialist physiotherapists or psychologists?
- When to refer to a pediatrician?

Multidisciplinary guideline "Constipation in children aged 0 to 18 years"

The MDR was last updated in 2015 and contains much information only important for pediatricians who treat complicated cases, and with 216 pages it is not suitable for use by professionals in primary care (GPs, public health pediatricians, physiotherapists). Nevertheless, coordination and, if necessary, adaptation of recommendations in the MDR are important if we want to provide effective and efficient care for children with FC, and to ensure that the right care is provided in the right setting. Consideration may be given to establishing a common and overarching guideline to which the guidelines of the various disciplines can be aligned.

Guideline "Toilet training for urine and feces" for public health pediatricians

In the Netherlands, all children (together with a parent) do have a regular consultation with a public health pediatrician around the age of 5 years. In this consultation the social-emotional and motor development is assessed, but also the functioning of hearing and vision. In addition, parents are asked whether their child is toilet trained for urine and feces. This means that questions about peculiarities around stool, e.g. changes in pattern and fecal incontinence are part of the routine care. With the knowledge that FC is an underestimated problem for which children and parents do not always seek medical help, it may be considered to give public health pediatricians a more prominent role in the early signaling of FC related symptoms in the child, by taking the ROME IV questionnaire for FC for each child. This may contribute to an earlier start of the treatment.

Future directions

Suggestions for further research have already been discussed above and in the previous chapters of this thesis. We have divided the recommendations for future research into three categories, namely recommendations related to 1) physiotherapy treatment for childhood FC, 2) the course of FC in primary care and 3) expectations and needs in the context of

treatment for FC.

1. Physiotherapy treatment for childhood FC

In the BOKi trial we have investigated the (cost-)effectiveness of physiotherapy added to conventional treatment compared to conventional treatment alone for children with FC in primary care.

- It is hypothesized that physiotherapy addresses, among other things, pelvic floor rehabilitation and changes in lifestyle and behavior, which take time to show effect. Therefore data on the long-term (cost-)effectiveness of physiotherapy are needed.
- Our subgroup analysis showed physiotherapy to be possibly (cost-)effective if symptoms were chronic. This warrants more research to investigate whether physiotherapy in primary care is (cost-)effective for children with symptoms of a longer duration.
- When physiotherapy is proven effective in children with chronic symptoms. Qualitative research is needed to examine which children and parents are willing to invest time and effort in physiotherapy, and what barriers and facilitators are for compliance with physiotherapy and for putting into practice what was learned during physiotherapy sessions.

2. Course of the FC

Little is known about the course of the FC in children seen in primary care.

- Data are needed on the course of FC in children consulting in primary care. How long, on average, do these children have symptoms? How many children develop long-term symptoms i.e. until adolescence or adulthood? Are there differences, in type of symptoms, onset, and course of the symptoms, between children treated in primary care and those referred to a specialist in the hospital?
- Which are factors associated with a prolonged course FC?

3. Expectations and needs in the context of treatment for FC

Many children do have FC related symptoms for a longer period of time before they (or their parents) seek medical help. In addition, the help of the GP is often limited to one consultation. The BOKi trial showed that symptoms may persist for more than 12 months. A long premedical phase and lack of follow up by the GP suggest lack of awareness of the impact and possibly long duration of FC. We need to better understand the expectations and needs of children, parents and GPs in the treatment of FC, to improve the management of FC in primary care. In addition, we need to better define the definition of treatment success to enhance the comparability of the (cost-)effectiveness of interventions for FC.

For this we need qualitative research:

- To examine the reasons for children and parents whether or not to seek medical help for FC and what they expect from the treatment.
- To examine what children and parents would define as successful treatment, what they consider as a realistic investment in time and efforts to reach a desired outcome, and if the investment in time and efforts will depend on the outcome of the treatment and the type and duration of symptoms.
- To investigate why the adherence to laxative treatment is low and how we can improve adherence.[30] Are children and parents afraid of harmful side-effects on the long-term, do children find it annoying to take the laxatives, is it difficult to maintain a regular schedule of the laxatives if symptoms seem to be resolved, are children and parents missing information related to the importance of regular use of laxatives or are children and parents worried whether there was an underlying medical cause for constipation etc.?
- To evaluate the current care pathway of children with FC, which health care professionals are involved in signaling FC related symptoms and performing the treatment. Is this in line with the clinical guidelines, for example is there sufficient time to give proper education and toilet training, and how might this be improved?

Overall conclusion

The BOKi trial showed that adding physiotherapy to conventional treatment for all children with FC in primary care cannot be considered as (cost-)effective treatment strategy. For children with chronic symptoms adding physiotherapy might be a valuable treatment strategy, but the subgroup of children with chronic symptoms in our trial was small and therefore further evaluation on the effectiveness and cost-effectiveness in this subgroup is needed. In addition, the BOKi trial showed that both a parent proxy-report and a child-self report can be used in research to measure the impact of the FC on the quality of life of the child. Nevertheless, clinicians are recommended to ask both the child and the parent(s) to get an impression of the impact of the FC on the quality of life because the assessment between parent-child pairs can vary significantly. Finally, this thesis showed that children with FC were more likely to have bladder symptoms compared to children without FC, and therefore physicians need to be alert to concurrent bladder problems in children with FC.

References

1. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. bmj 2015; 350.
2. Dal-Ré R, Janiaud P, Ioannidis JP. Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic? BMC medicine 2018; 16(1): 1-6.
3. Kuizenga-Wessel S, Heckert SL, Tros W, van Etten-Jamaludin FS, Benninga MA, Tabbers MM. Reporting on outcome measures of functional constipation in children—a systematic review. Journal of pediatric gastroenterology and nutrition 2016; 62(6): 840-6.
4. Koppen I, Saps M, Lavigne J, et al. Recommendations for pharmacological clinical trials in children with functional constipation: The Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterology & Motility 2018; 30(4): e13294.
5. Thompson AP, Wine E, MacDonald SE, Campbell A, Scott SD. Parents' Experiences and Information Needs While Caring for a Child With Functional Constipation: A Systematic Review. Clin Pediatr (Phila) 2021; 60(3): 154-69.
6. Kuizenga-Wessel S, Steutel NF, Benninga MA, et al. Development of a core outcome set for clinical trials in childhood constipation: a study using a Delphi technique. BMJ paediatrics open 2017; 1(1).
7. Van Summeren JJ, Holtman GA, Dekker JH, Berger MY. Quality of life in children with functional constipation: Are child self-reports and parent proxy-reports interchangeable? The Journal of pediatrics 2020; 217: 216.
8. Voskuijl WP, van der Zaag-Loonen HJ, Ketel I, Grootenhuis MA, Derkx B, Benninga MA. Health related quality of life in disorders of defecation: the Defecation Disorder List. Archives of disease in childhood 2004; 89(12): 1124-7.
9. Bongers ME, Benninga MA, Maurice-Stam H, Grootenhuis MA. Health-related quality of life in young adults with symptoms of constipation continuing from childhood into adulthood. Health and Quality of Life Outcomes 2009; 7(1): 1-9.
10. Wille N, Badia X, Bonsel G, et al. Development of the EQ-5D-Y: a child-friendly version of the EQ-5D. Quality of life research 2010; 19(6): 875-86.
11. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes: Oxford university press; 2015.
12. Knies S, Evers SM, Candel MJ, Severens JL, Ament AJ. Utilities of the EQ-5D: transferable or not? Pharmacoeconomics 2009; 27(9): 767-79.
13. Vriesman MH, Koppen IJ, Camilleri M, Di Lorenzo C, Benninga MA. Management of functional constipation in children and adults. Nature Reviews Gastroenterology & Hepatology 2020; 17(1): 21-39.

14. Tabbers M, DiLorenzo C, Berger M, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. Journal of pediatric gastroenterology and nutrition 2014; 58(2): 258-74.
15. Rowan-Legg A, Society CP, Committee CP. Managing functional constipation in children. Paediatrics & child health 2011; 16(10): 661-5.
16. Nederlands Huisartsen Genootschap. NHG standard obstipatie [Internet]. [cited 2021, Nov 19]. Available from: https://richtlijnen.nhg.org/standaarden/obstipatie#volledige-teksthttps://richtlijnen.nhg.org/standaarden/obstipatie#volledige-tekst.
17. Nederlandse Vereniging voor Kindergeneeskunde, Nederlands Huisarts Genootschap. Richtlijn obstipatie bij kinderen van 0 tot 18 jaar [Internet]. [cited 2021, Nov 19]. Available from: https://richtlijnendatabase.nl/richtlijn/obstipatie_bij_kinderen_van_0_tot_18_jaar/obstipatie_- _startpagina.html
18. Thompson AP, MacDonald SE, Wine E, Scott SD. Understanding Parents' Experiences When Caring for a Child With Functional Constipation: Interpretive Description Study. JMIR pediatrics and parenting 2021; 4(1): e24851.
19. Pijpers MA, Tabbers M, Benninga MA, Berger MY. Currently recommended treatments of childhood constipation are not evidence based: a systematic literature review on the effect of laxative treatment and dietary measures. Archives of disease in childhood 2009; 94(2): 117-31.
20. Bongers ME, van Wijk MP, Reitsma JB, Benninga MA. Long-term prognosis for childhood constipation: clinical outcomes in adulthood. Pediatrics 2010; 126(1): e156-e62.
21. Tang J, Li H, Tang W. Efficacy of Non-pharmacologic Auxiliary Treatments in Improving Defecation Function in Children With Chronic Idiopathic Constipation: A Systematic Review and Network Meta-analysis. Front Pediatr 2021; 9: 667225-.
22. Wegh CAM, Baaleman DF, Tabbers MM, Smidt H, Benninga MA. Nonpharmacologic Treatment for Children with Functional Constipation: A Systematic Review and Meta-analysis. The Journal of Pediatrics 2021.
23. Timmerman ME, Trzpis M, Broens PM. The problem of defecation disorders in children is underestimated and easily goes unrecognized: a cross-sectional study. European journal of pediatrics 2019; 178(1): 33-9.
24. Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. Journal of pediatric gastroenterology and nutrition 2010; 50(3): 256-68.
25. Averbeck MA, Madersbacher H. Constipation and LUTS: how do they affect each other? International braz j urol 2011; 37: 16-28.
26. Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem. World journal of gastroenterology 2016; 22(30):

6864.
27. Kaplan S, Dmochowski R, Cash B, Kopp Z, Berriman S, Khullar V. Systematic review of the relationship between bladder and bowel function: implications for patient management. International journal of clinical practice 2013; 67(3): 205-16.
28. Malykhina A. Neural mechanisms of pelvic organ cross-sensitization. Neuroscience 2007; 149(3): 660-72.
29. Thuisarts.nl. Mijn kind heeft last van verstopping [Internet]. [cited 2021, Nov 19]. Available from: https://www.thuisarts.nl/verstopping/mijn-kind-heeft-last-van-verstopping
30. Koppen IJN, van Wassenaer EA, Barendsen RW, Brand PL, Benninga MA. Adherence to polyethylene glycol treatment in children with functional constipation is associated with parental illness perceptions, satisfaction with treatment, and perceived treatment convenience. The Journal of pediatrics 2018; 199: 132-9. e1.
31. Nederlands Centrum Jeugdgezondheid. Richtlijn: zindelijkheid van urine en feces [Internet}. [Cited 2021, Nov 19]. Available from: https://www.ncj.nl/richtlijnen/alle-richtlijnen/richtlijn/?richtlijn=19&rlpag=779

Letters to the editor

Pelvic Physiotherapy in Children With Functional Constipation: Promising But More Research Needed

Dear Editors:

We congratulate van Engelenburg-van Lonkhuyzen et al[1] on their study on the effectiveness of pelvic physiotherapy in children with functional constipation. This randomized, controlled trial showed that pelvic physiotherapy was more effective than standard medical care in the treatment of children with constipation after 6 months of follow-up. This is the first study exploring a promising nonpharmacologic treatment for functional constipation in children with a longer follow-up. The results are in line with an earlier study by Silva et al[2] that showed a significantly positive effect of a 6-week physiotherapy program on defecation frequency.

Unfortunately, van Engelenburg-van Lonkhuyzen et al[1] could include only 53 of the targeted 367 children, which means that their findings need to be interpreted with caution. Owing to the small sample size, there is the danger of a type I error, namely, that a statistically significant difference between the 2 treatment groups would not have been found if the sample size had been as calculated before the start of the study (false-positive result). The authors report the chance of a type I error is small because all primary and secondary outcomes, with the exception of the SDQ, showed significant results favoring pelvic physiotherapy, the dropout rate in the trial was lower than expected, and the absolute risk reduction in the trial was 30% instead of 15% used in the power calculation. However, small and underpowered studies can only detect significant effects that happen to be large. Therefore, even when the significant effect found in this study is not a false-positive result, it is likely the estimate of the magnitude of the effect is exaggerated (winner's curse).[3]

The authors showed that 92.3% of the children undergoing pelvic physiotherapy and 63% of the children receiving standard medical care had been treated successfully after 6 months. This means an absolute risk reduction of 29.3% with a 95% confidence interval (CI) of 0.07%– 48.8%. The wide CI shows a lack of precision in estimating the effect of the intervention. This means that the possibility that the effect will be less than the 15% risk reduction the authors considered of clinical relevance, is considerable. Nevertheless, the results of this trial are encouraging and invite more research in this relevant field. Before we can recommend pelvic physiotherapy as an effective treatment in childhood constipation, we need larger studies to verify the findings of van Engelenburg-van Lonkhuyzen et al.[1]

One other point concerns the acceptability of the intervention: in their manuscript on the design of the study, the authors described a pelvic physiotherapy protocol that included muscle assessment by rectal examination, myofeedback, and rectal balloon training.[4] However, 28 of the 53 children (52.8%) refused pelvic floor muscle assessments at baseline and 36 children (67.9%) refused pelvic floor muscle assessments at follow-up. The authors do not report more detailed information on the number of children receiving myofeedback and rectal balloon training, nor do they report the number of sessions in which these aspects of treatment were included. Detailed information on this is important because myofeedback and rectal balloon training are burdensome for children and, if most of them refuse it, we think it should be reconsidered whether it should be part of a therapeutic intervention in functional childhood constipation. In addition, either adding or omitting these aspects of therapy will influence the choice of competences of the professional giving the physiotherapy.

Jojanneke van Summeren
Janny Dekker
Marjolein Berger

References

1. van Engelenburg-van Lonkhuyzen ML, et al. Gastroenterology 2017;152:82–91.
2. Silva C, et al. Colorectal Dis 2013;15:e250–e255.
3. Button KS, et al. Nat Rev Neurosci 2013;14:365–376.
4. van Engelenburg-van Lonkhuyzen ML, et al. BMC Pediatr 2013;13:112.

Quality of life in children with functional constipation: Are child self-reports and parent proxy-reports interchangeable?

To the Editor:

We thank Vriesman et al for providing an extensive overview of the health-related quality of life (HRQoL) of children with functional constipation.[1] HRQoL is identified as an important outcome when evaluating the effect of a treatment in both clinical trials and the doctor's office.[2,3] As mentioned by the authors, there is substantial debate who is the most appropriate respondent to assess children's HRQoL: the child itself or the parent(s).[4] To examine the parent–child agreement, the authors compared the total HRQoL scores on the Pediatric Quality of Life Inventory questionnaire reported by children and parents and suggested that the scores were quite similar, with a score of 62.03 (SD 11.46) and 64.95 (SD 12.99), respectively, so there seems to be good parent– child agreement on a group level. Therefore, they suggest that both parent proxy-reports as child self-reports can be used in a clinical setting, but they emphasize the need of large cohort studies.

We published a study investigating parent–child agreement on HRQoL in children with functional constipation (n = 56), aged 8-17 years.[5] Just as Vriesman et al, we found a good parent–child agreement on a group level; intraclass correlation coefficient of 0.80 (95% CI 0.67-0.88) and 0.78 (95% CI 0.65-0.87) for the Defecation Disorder List and EuroQol-5-Dimension-Yourth Visual Analogue Scale, respectively. However, we found considerable discordance on HRQoL between individual parent–child pairs. The limits of agreement of the Bland–Altman plots were 19.7 and 14.6 for the Defecation Disorder List and 27.6 and 21.8 for the EuroQol-5-Dimension-Yourth Visual Analogue Scale, on a range of a 0 to 100 score on both questionnaires. Age and sex of the child were not associated with parent–child agreement. Therefore, we advise clinicians to pay attention to both the child's and parent's perception of the child's HRQoL.

Jojanneke van Summeren
Gea Holtman
Janny Dekker
Marjolein Berger

References

1. Vriesman MH, Rajindrajith S, Koppen IJ, van Etten-Jamaludin FS, van Dijk M, Devanarayana NM, et al. Quality of life in children with functional constipation: a systematic review and meta-analysis. J Pediatr 2019;214:141-50.
2. Tabbers MM, DiLorenzo C, Berger MY, Faure C, Langendam MW, Nurko S, et al. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr 2014;58:258-74.
3. Koppen IJN, Saps M, Lavigne JV, Nurko S, Taminiau JAJM, DiLorenzo C, et al. Recommendations for pharmacological clinical trials in children with functional constipation: the Rome foundation pediatric subcommittee on clinical trials. Neurogastroenterol Motil 2018;30:e13294.
4. Wallander JL, Koot HM. Quality of life in children: a critical examination of concepts, approaches, issues, and future directions. Clin Psychol Rev 2016;45:131-43.
5. van Summeren JJGT, Klunder JW, Holtman GA, Kollen BJ, Berger MY, Dekker JH. Parent–child agreement on health-related quality of life in children with functional constipation in primary care. J Pediatr Gastroenterol Nutr 2018;67:726-31.

Nederlandse samenvatting

Nederlandse samenvatting

Het doel van dit promotietraject is onderzoeken of het toevoegen van kinderbekkenfysiotherapie, aan de behandeling van functionele obstipatie bij kinderen in de leeftijd van 4 t/m 18 jaar, (kosten) effectiever is dan alleen de behandeling van de huisarts. Daarvoor is de BOKi studie (**B**ehandeling van **O**bstipatie bij **Ki**nderen) opgezet en uitgevoerd. Daarnaast hebben we onderzocht of kinderen en ouders dezelfde perceptie hebben over de impact van de functionele obstipatie op de kwaliteit van leven van het kind. Als laatste hebben we aan de hand van een literatuuronderzoek onderzocht hoe vaak plasklachten en urineweginfecties voorkomen bij kinderen met functionele obstipatie.

In deze samenvatting worden de achtergrond, de opzet van de BOKi studie, de belangrijkste bevindingen uit de BOKi studie en de aanvullende onderzoeken en de algemene conclusies en aanbevelingen voor de praktijk in begrijpelijk Nederlands uitgelegd.

Achtergrond

Functionele obstipatie is obstipatie waarvoor geen organische verklaring is. Het is een veelvoorkomende aandoening bij kinderen en kan een grote impact hebben op de kwaliteit van leven. Symptomen van functionele obstipatie zijn onder andere: minder dan 3 keer per week ontlasting, ophoping van ontlasting in het rectum, een pijnlijke stoelgang, incontinentie voor ontlasting en het ophouden van ontlasting. Kinderen komen vaak in een vicieuze cirkel terecht: het ophouden van ontlasting heeft tot gevolg dat de ontlasting harder wordt omdat het water aan de ontlasting wordt onttrokken, wat leidt tot een grote hoeveelheid ontlasting in de darm, waardoor de stoelgang moeilijker en pijnlijker wordt en als gevolg daarvan houden kinderen de ontlasting vaker op etc.

Het chronische karakter en de impact van de symptomen die horen bij functionele obstipatie worden vaak onderschat door zowel het kind als de ouder(s), maar ook door medische professionals zoals de huisarts. In de richtlijnen die huisartsen gebruiken voor het behandelen van functionele obstipatie wordt geadviseerd om te starten met uitleg over de functionele obstipatie en het geven van voedingsadviezen en toilettraining. Als de symptomen niet verbeteren wordt geadviseerd om te starten met laxantia. Ondanks behandeling met laxantia heeft ongeveer de helft van de kinderen 6 tot 12 maanden na de start van de behandeling nog steeds symptomen die passen bij functionele obstipatie. Vijfentwintig procent van de kinderen heeft nog steeds symptomen als ze volwassen zijn.

Het BOKi onderzoek

Functionele obstipatie bij kinderen heeft een multifactoriële etiologie, dit betekent dat verschillende factoren een rol kunnen spelen, onder andere: ophoudgedrag, het onjuist aan- en/of ontspannen van de bekkenbodemspieren, een verkeerde toilettraining en omgevingsfactoren (bijvoorbeeld verandering van school, onwennige school wc, pesten en gezinsproblemen). Eerder onderzoek laat positieve resultaten zien van het toevoegen van kinderbekkenfysiotherapie aan de behandeling van kinderen met functionele obstipatie die in het ziekenhuis onder behandeling zijn. Kinderbekkenfysiotherapie richt zich op het juist aanleren van het aan- en ontspannen van de bekkenbodemspieren tijdens de toiletgang, maar heeft ook aandacht voor de multifactoriële etiologie van functionele obstipatie. De hypothese is dat chronische functionele obstipatie voorkomen kan worden als de behandeling al bij de eerste klachten begint. Daarom hebben we het BOKi onderzoek opgezet, waarin de volgende onderzoeksvraag onderzocht is: "Is het toevoegen van kinderbekkenfysiotherapie aan de standaardbehandeling van functionele obstipatie bij kinderen (4 tot en met 17 jaar) in de huisartsenpraktijk een (kosten) effectievere behandelstrategie dan alleen de standaardbehandeling door de huisarts".

In **hoofdstuk 2** van dit proefschrift hebben we het onderzoeksdesign van het BOKi onderzoek beschreven. Het BOKi onderzoek is een gerandomiseerde gecontroleerde studie met een follow-up duur 8 maanden. De huisarts nodigde kinderen met functionele obstipatie die voldeden aan de inclusie criteria uit om deel te nemen. Deze inclusie criteria waren 1) leeftijd 4 t/m 17 jaar en 2) een diagnose functionele obstipatie gesteld door de huisarts. Kinderen (en hun ouders) die in de afgelopen 12 maanden de huisarts hadden bezocht met functionele obstipatie kregen een vragenlijst waarin werd gekeken of het kind in de afgelopen 4 weken nog klachten had of laxantia gebruikte. Zo ja, dan werd het kind (en de ouders) uitgenodigd om deel te nemen aan het BOKi onderzoek. De helft van de kinderen kreeg naast de standaardbehandeling door de eigen huisarts een verwijzing voor kinderbekkenfysiotherapie (fysiotherapiegroep), de andere helft kreeg alleen de standaardbehandeling van de huisarts (standaardzorggroep). De kinderbekkenfysiotherapeut is speciaal opgeleid om onder andere functionele obstipatie bij kinderen te behandelen. De primaire uitkomstmaat van het onderzoek was behandelsucces, gedefinieerd als afwezigheid van functionele obstipatie en geen gebruik van laxantia. De secundaire uitkomstmaten waren 1) behandelsucces gedefinieerd als afwezigheid van functionele obstipatie ongeacht het gebruik van laxantia, 2) kwaliteit van leven en 3) globaal ervaren behandeleffect, dit is een maat om verbetering van de klachten te meten. De (kosten) effectiviteit van kinderbekkenfysiotherapie is ook onderzocht in een vooraf bepaalde subgroep van kinderen met chronische obstipatie. Chronische obstipatie is in dit onderzoek gedefinieerd als het continu of regelmatig (≥3 periodes) gebruik van laxantia in de

12 maanden voor deelname aan het onderzoek. In totaal zijn er 134 kinderen in de leeftijd van 4 tot en met 17 jaar gerandomiseerd in één van de twee behandelgroepen (67 kinderen per groep).

De resultaten van het BOKi onderzoek worden beschreven in **hoofdstuk 3 en 4**. Na 8 maanden was 42% van de kinderen in de fysiotherapiegroep en 41% van de kinderen in de standaardzorg groep succesvol behandeld volgens de primaire definitie van behandelsucces. Voor de secundaire definitie van behandelsucces was dit respectievelijk 73% en 61%. Kinderbekkenfysiotherapie toegevoegd aan de standaardbehandeling van de huisarts had niet significant meer behandelsucces dan alleen de standaardbehandeling van de huisarts volgens beide definities van behandelsucces en ook de verandering in de kwaliteit van leven verschilde niet tussen de twee groepen (**hoofdstuk 3**). In tegenstelling tot deze bevindingen rapporteerden significant meer ouders van de kinderen in de fysiotherapiegroep een verbetering van de klachten (62%) dan ouders in de standaardzorggroep (52%). In de subgroep van kinderen met chronische obstipatie (n=72) werd significant vaker behandelsucces (gedefinieerd als geen functionele obstipatie ongeacht het gebruik van laxantia) vastgesteld in de fysiotherapiegroep (83%) dan in de standaardzorggroep (48%). Op de andere 3 uitkomstmaten, primaire definitie van behandelsucces (gedefinieerd als geen functionele obstipatie en geen laxantia), kwaliteit van leven en globaal ervaren behandeleffect werd geen significant verschil gevonden tussen de twee behandelgroepen. De conclusie uit het BOKi onderzoek is dat het toevoegen van kinderbekkenfysiotherapie aan de standaardzorg geen effectieve behandelstrategie is voor alle kinderen met functionele obstipatie in de huisartsenpraktijk. Onze subgroep analyse suggereert echter dat kinderbekkenfysiotherapie effectief zou kunnen zijn voor kinderen met chronische klachten, maar dit moet verder worden onderzocht in een groter gerandomiseerd onderzoek.

We hebben ook een kosteneffectiviteitsanalyse (KEA) uitgevoerd vanuit een maatschappelijk perspectief (**hoofdstuk 4**). Een KEA is waardevol ondanks dat in hoofdstuk 3 is aangetoond dat er geen significant verschil was in behandelsucces tussen de twee behandelgroepen. Het gaat in een KEA namelijk om het evenwicht tussen kosten en effecten. Daarnaast kan er een verschil in kosten tussen de twee behandelgroepen bestaan. De gemiddelde maatschappelijke kosten per kind in de fysiotherapiegroep waren €155 euro (95% BI €-12 tot €310) hoger in vergelijking met de gemiddelde kosten in de standaardzorggroep. De incrementele kosteneffectiviteitsratio (ICER) is een maat om de kosten uit te drukken om één extra kind succesvol te behandelen. Voor behandelsucces gedefinieerd als afwezigheid van klachten en geen gebruik van laxantia' was de ICER €24.060 (95% BI €-16.275 tot €31.390). Voor behandelsucces gedefinieerd als 'afwezigheid van klachten ongeacht het gebruik van laxantia' was de ICER €1.221 (95% BI €-12.905 tot €10.956). Er is geen bedrag vastgesteld

dat de maatschappij bereid is om te betalen om één extra kind succesvol te behandelen. Daardoor is het moeilijk om harde conclusies te trekken over de kosteneffectiviteit van kinderbekkenfysiotherapie toegevoegd aan de standaardbehandeling in vergelijking met alleen de standaardbehandeling van de huisarts. Echter, ongeacht het bedrag dat de maatschappij bereid zou zijn te betalen is de kans dat kinderbekkenfysiotherapie toegevoegd aan de standaardbehandeling kosteneffectiever is dan alleen de standaardbehandeling niet groter dan 50% volgens de primaire definitie van behandelsucces en 90% voor de secundaire definitie van behandelsucces. Daarom concluderen we dat het toevoegen van kinderbekkenfysiotherapie aan de standaardbehandeling van de huisarts niet als kosteneffectief kan worden beschouwd ten opzichte van de standaardbehandeling. Voor de subgroep van kinderen met chronische functionele obstipatie zijn de kosten lager om één extra kind succesvol te behandelen, respectievelijk €2.134 (95%BI €-24.975 tot €17.192) en €571 (95%CI €11 tot €3.566). De subgroep van kinderen met chronische functionele obstipatie was klein en daarom is verder onderzoek naar de (kosten) effectiviteit van kinderbekkenfysiotherapie voor kinderen met functionele obstipatie nodig.

Belangrijkste bevindingen aanvullende onderzoeken

Kwaliteit van leven is een belangrijke maat om de impact van een ziekte op het welzijn van een patiënt te bepalen. Deze maat wordt niet alleen vaak in onderzoek gebruikt, maar maakt ook deel uit van de dagelijkse praktijk van huisartsen en andere zorgprofessionals. Het meten van de kwaliteit van leven bij kinderen is gecompliceerd omdat er veel discussie is over de meest geschikte respondent voor het beoordelen van de kwaliteit van leven: het kind zelf of de ouder(s). In **hoofdstuk 5** hebben we gekeken naar de overeenkomst in de kwaliteit van leven van kinderen met functionele obstipatie, in de leeftijd van 8 tot en met 17 jaar, gerapporteerd door het kind zelf en de ouder(s). Hiervoor hebben we 2 verschillende baseline vragenlijsten gebruikt: de Defecation Disorder List (DDL) en de Visueel Analogische Schaal uit de EuroQol-5-dimensies-jeugd vragenlijst (VAS-EQ5D-Y). De DDL is een ziektespecifieke kwaliteit van leven vragenlijst en de VAS-EQ5D-Y een vraag over de algemene gezondheidsstatus van het kind. In het onderzoek is aangetoond dat op groepsniveau de overeenkomsten tussen ouder en kind op beide vragenlijsten goed is. Dit betekent dat zowel een vragenlijst ingevuld door de ouder(s) als door het kind zelf, gebruikt kan worden om de kwaliteit van leven te meten in onderzoek. Een deel van de ouder-kind paren verschilde echter aanzienlijk in hun beoordeling van de kwaliteit van leven van het kind, waarbij leeftijd en geslacht niet geassocieerd waren met het niveau van overeenstemming tussen ouder en kind. Daarom raden we huisartsen en andere zorgprofessionals aan om zowel het kind als de ouder(s) te bevragen om een indruk te krijgen van de impact van de functionele obstipatie op de kwaliteit van leven van het kind.

Poep- en plasproblemen komen volgens de literatuur bij kinderen vaak samen, maar de daadwerkelijke omvang van plasproblemen bij kinderen met functionele obstipatie is onbekend. In een systematisch literatuuronderzoek (**hoofdstuk 6**) hebben we 23 studies geïncludeerd die rapporteerden over de prevalentie van plasproblemen bij kinderen met functionele obstipatie. Tweeëntwintig studies (12.281 kinderen met functionele obstipatie) rapporteerden over klachten van de lagere urinewegen (LUTS) en zeven studies (687 kinderen met functionele obstipatie) rapporteerden over urineweginfecties (UWI). Er was veel heterogeniteit in de gebruikte definities voor LUTS klachten en functionele obstipatie en daarom hebben we besloten dat het niet zinvol was om gepoolde schattingen te maken van de prevalentie van plasproblemen bij kinderen met functionele obstipatie. De prevalentie van LUTS (gedefinieerd als een maat voor alle LUTS klachten samen) bij kinderen met functionele obstipatie varieerde van 37% tot 64% (3 studies). De prevalentie van enkelvoudige LUTS symptomen varieerde van 2% voor het symptoom "gespannen bekkenbodemspieren" tot 47% voor bedplassen. UWI's werden gerapporteerd in 6% tot 53% van de kinderen met functionele obstipatie.

In 12 van de 23 studies werden plasproblemen gemeten bij zowel kinderen met functionele obstipatie als in een controlegroep van kinderen zonder functionele obstipatie. Hierdoor kunnen de prevalentie cijfers tussen de twee groepen vergelijken worden. Twee van de 12 studies hanteerden een maat voor alle LUTS symptomen samen. Deze studies toonden aan dat kinderen met functionele obstipatie significant vaker LUTS klachten hadden in vergelijking met kinderen zonder functionele obstipatie. Tien andere studies vergeleken de prevalentie van een of meer afzonderlijke LUTS symptomen tussen kinderen met en zonder functionele obstipatie (in totaal werden er 18 vergelijkingen gemaakt in de 10 studies). Kinderen met functionele obstipatie hadden een significant hoger risico op LUTS in vergelijking met kinderen zonder functionele obstipatie in 12 van de 18 vergelijkingen. De twee studies die het percentage UWI's vergeleken tussen kinderen met en zonder functionele obstipatie toonden geen significante verschillen tussen beide groepen. De steekproefgrootte in beide studies was echter klein (<50 kinderen). Gezien de hoge prevalentie van LUTS symptomen bij kinderen met functionele obstipatie, raden we huisartsen en kinderartsen aan om actief te vragen naar LUTS klachten bij kinderen met functionele obstipatie.

Algemene conclusies en aanbevelingen voor de praktijk

Het BOKi onderzoek en de aanvullende studies laten zien dat functionele obstipatie klachten vaak langdurig aanhouden. In de huisartsenpraktijk is het standaard toevoegen van kinderbekkenfysiotherapie aan de behandeling van kinderen met functionele obstipatie geen (kosten)effectieve behandelstrategie. Voor kinderen met chronische functionele obstipatie kan de huisarts, in overleg met het kind en de ouders, een verwijzing naar een

kinderbekkenfysiotherapeut overwegen. Verdere evaluatie van de (kosten)effectiviteit van kinderbekkenfysiotherapie voor kinderen met chronische functionele obstipatie is belangrijk omdat deze subgroep in ons onderzoek klein was. Huisartsen en andere zorgprofessionals wordt aanbevolen om zowel aan het kind als de ouder(s) te vragen wat de impact is van de functionele obstipatie op de kwaliteit van leven van het kind, omdat er aanzienlijke verschillen kunnen zijn in de perceptie van het kind en de ouder(s). Als laatste blijkt uit dit onderzoek dat kinderen met functionele obstipatie vaker plasproblemen hebben dan kinderen zonder functionele obstipatie, daarom adviseren we huisartsen en andere zorgprofessionals om expliciet te vragen naar plasproblemen bij kinderen met functionele obstipatie.

De multifactoriële aanpak van functionele obstipatie beschreven in richtlijnen voor huisartsen en kinderartsen komt overeen met de aanbevelingen die worden beschreven in **hoofdstuk 7** van dit proefschrift. In de praktijk worden deze aanbevelingen uit de richtlijnen echter niet altijd goed opgevolgd. Huisartsen zien functionele obstipatie bijvoorbeeld nog te vaak als een symptoom dat behandeld kan worden met laxantia, in plaats van een chronische aandoening. Tijd voor een uitgebreide uitleg over de functionele obstipatie en de vicieuze cirkel waarin kinderen terecht kunnen komen, het geven van toilettraining en het geven van voedingsadviezen ontbreekt vaak. De ernst van de functionele obstipatie wordt daardoor regelmatig onderschat door zowel het kind als de ouders. Het advies aan huisartsen is om de functionele obstipatie actief te monitoren en ook het kind en/of de ouders (afhankelijk van de leeftijd van het kind) uitleg te geven over het actief herkennen en monitoren van de symptomen.

Om kinderen met functionele obstipatie vroegtijdig te herkennen en behandelen is het belangrijk dat de verschillende betrokken zorgprofessionals, zoals huisartsen, jeugdartsen, kinderartsen en kinderbekkenfysiotherapeuten, de verdeling en coördinatie van de taken beter op elkaar afstemmen. Een gemeenschappelijke overkoepelende richtlijn met aanbevelingen voor het vroegtijdig herkennen en behandelen van kinderen met functionele obstipatie zou een leidraad kunnen zijn voor de aanbevelingen in de richtlijnen voor de verschillende disciplines.

Dankwoord

About the author

Dankwoord

Get shit done; dat is waar dit hele proefschrift om draait. Letterlijk en figuurlijk. Het was een rollercoaster aan hoogte en dieptepunten. Ik wil graag de mensen bedanken die me inhoudelijk en daaromheen hebben geholpen en gesteund.

Zonder deelnemers en data geen onderzoek, daarom gaat mijn dank uit aan alle kinderen, ouders, huisartsen, kinderartsen en kinderbekken-fysiotherapeuten die mee hebben gedaan aan het BOKi onderzoek. Een speciaal woord van dank aan de kinderbekkenfysiotherapeuten die hebben geholpen met het opstellen van het kinderbekkenfysiotherapie behandelprotocol.

Prof. Dr. M.Y. Berger, beste Marjolein, in de afgelopen acht jaren heb ik veel van jou mogen leren en genoten van jouw enthousiasme over wetenschap, methodologie en allerlei nieuwe onderzoeksideeën. Ondanks dat het voor jou soms zoeken was naar tijd om mijn manuscripten te lezen, ik zal niet ontkennen dat mijn geduld soms aardig op de proef werd gesteld, waren onze discussies en jouw kritische feedback altijd heel waardevol. Hierdoor ben ik gegroeid als onderzoeker. Ook heb ik veel geleerd van jouw klinische blik bij het schrijven van artikelen en het opzetten van onderzoek, dit is iets wat ik zal blijven meenemen in het vervolg van mijn carrière!

Dr. J.H. Dekker, beste Janny, ik ben jouw laatste promovendus. Heel erg bedankt voor de altijd snelle, fijne en duidelijke feedback. Ik ben heel blij dat jij de rol van dagelijks begeleider hebt overgenomen ondanks dat je officieel (bijna) met pensioen was. Nu is mijn proefschrift klaar. Dit was zeker niet gelukt zonder jouw volhardendheid. Zeker de laatste jaren stuurde je op zijn tijd een mailtje als je alweer even niets van me had gehoord. Het leek wel of je wist dat ik op die momenten aan het worstelen was met mijn drang naar perfectie. Jouw aanmoediging zorgde ervoor dat ik een deadline voor mezelf durfde te stellen voor het rondsturen van een nieuwe versie van mijn manuscript. Ik ben blij dat ik met jouw hulp ook deze kant van mezelf heb kunnen ontwikkelen.

Dr. G.A. Holtman, beste Gea, we begonnen als kamergenoten en mede-promovendi. Na

jouw promoveren ben jij toegevoegd aan mijn promotieteam. Als kamergenoten zaten we regelmatig zo in de flow dat we zonder dat we het door hadden de laatste waren die de afdeling verlieten. Het was heel fijn om met jou laagdrempelig te kunnen sparren over praktische zaken zoals het werven van deelnemers, het enthousiasmeren van huisartsen en het maken van een poster voor een congres. Maar ook over inhoudelijke zaken zoals het structureren van artikelen. Ik hoop dat er nog vele wandelingen volgen waarbij we onze te bewandelen weg in de wetenschappelijke wereld bespreken.

De leden van de beoordelingscommissie, Prof. dr. M.A. Benninga, Prof. dr. A. Vermandel en Prof. Dr. N. Scherpbier-de Haan, wil ik graag hartelijk bedanken voor hun bereidheid dit proefschrift te lezen en te beoordelen.

Alle medeauteurs wil ik bedanken voor de bijdrage aan de artikelen, in het bijzonder wil ik een paar mensen noemen. Alice van Ulsen-Rust, jij bent een echte inspirator, van jou heb ik veel geleerd over het werk van kinderbekkenfysiotherapeuten. Bedankt dat jij me hebt voorgesteld aan mensen uit jouw netwerk, op deze manier hebben we samen ons onderzoek zichtbaar gemaakt in het werkveld, zowel in Nederland als daarbuiten. Yvonne Lisman-van Leeuwen, jouw motivatiekaartjes liggen nog steeds op mijn bureau ter inspiratie bij een writer's block. Lisa Louer, jouw inzet en hulp bij de uitvoering van de logistiek van het BOKi onderzoek waren onmisbaar. Boudewijn Kollen, bedankt voor alle hulp met het uitvoeren van de statistische analyses, ik heb veel van je geleerd. Karin Vermeulen, jij was de rots in de branding bij de uitvoering van de KEA analyse, door jou ben ik geïnspireerd geraakt in het doen van kosten evaluaties in gezondheidsonderzoek.

De studenten geneeskunde die hun wetenschappelijke stage hebben voltooid bij de BOKi studie, Martine, Lisette, Sonja en Jan Willem, bedankt dat jullie hebben geholpen met de logistiek van het BOKi onderzoek. Ik hoop dat jullie net zoveel hebben geleerd van mij als ik van jullie. Sonja en Jan Willem, jullie stageverslag was het begin van 2 artikelen in mijn proefschrift.

Beste Jan Schuling en Floor Haaijer-Ruskamp, bedankt dat jullie mij de ruimte hebben gegeven om te starten met mijn promotieonderzoek en het PROM onderzoek in deeltijd af te ronden. Ik ben trots dat we samen 2 mooie artikelen uit dit onderzoek hebben gepubliceerd, de allereerste 2 artikelen uit mijn wetenschappelijke carrière.

Alle collega's van de afdeling huisartsgeneeskunde wil ik bedanken voor de leuke inhoudelijke discussies over methodologische kwesties en de maatschappelijke relevantie van ons onderzoek. De koffiepauzes waren een gelegenheid om te ontspannen, maar ook een bron

van inspiratie voor nieuwe onderzoeksideeën en de jaarlijkse retraite op Schier was altijd iets om naar uit te kijken. Marco, jij was mijn programmaleider en maakte altijd ruimte voor het beantwoorden van vragen of om inhoudelijk te sparren, bedankt dat je me twee keer hebt meegenomen naar het ICS congres. Heleen, Marjolein, Gea, Anne, Nienke, Henriette, Janny, Marco, Grietje, Francoise en Miranda, zonder jullie waren de congressen in Londen, Genève, Florence en Gotenburg een stuk minder leuk geweest. Ik denk nog vaak terug aan de wandelingen door het park, gezellig samen uit eten, sjieke gala diners waarbij flink werd gedanst, chianti in een plastic beker en het fietsen door de heuvels van Toscane.

Gelukkig is er meer in het leven dan alleen onderzoek, vrienden bedankt voor de ontspanning en het lachen tijdens alle etentjes, biertjes, wijntjes, skivakanties en pasjes in de kroeg. Lieve dames van Sjaak en de Clubdames bedankt voor alle gezelligheid en afleiding tijdens onze weekendjes weg, uitjes en etentjes. Ondanks dat we door het hele land wonen hoop ik dat we nog lang vriendinnen blijven. Rosan, Gwen, Caro, Selma, Akkelien en Renee jullie wonen het dichtste bij en hebben daarom het vaakst geluisterd naar mijn struggles met het afronden van dit proefschrift! Heel erg bedankt voor al jullie bemoedigende woorden! Het is me gelukt, het proefschrift is af!

In november 2019 ben ik bij het Nivel gestart aan een nieuw onderzoeksproject. Beste John Paget, Michel Duckers en Joke Korevaar, bedankt dat jullie mij de mogelijkheid hebben gegeven om mezelf verder te ontwikkelen als onderzoeker. Daarnaast wil ik alle andere collega's uit het RAM IZB team (Lisa, Jacob, Lotte, Mandy en Marco) en het RSV ComNet team (Mariette en Janneke), mijn kamergenoten (Karin, Linda en Tessa) en de overige trouwe leden van het Nivel plank groepje (Lotte, Willemijn, Marianne en Leontien) bedanken dat jullie me zo snel hebben laten thuis voelen op het Nivel en er (waarschijnlijk onbewust) aan hebben bijgedragen dat ik het plezier in het doen van onderzoek weer heb teruggevonden. Lisa, Lotte en Jacob heel veel succes met (het afronden van) jullie promotie onderzoek. Ik kijk ernaar uit om jullie te zien stralen tijdens jullie verdediging in het Academiegebouw in het mooie Groningen! Als jullie nog Groningen tips nodig hebben weten jullie me te vinden.

Arnoud bedankt voor het maken van de lay-out van het proefschrift en er samen met Pepijn voor te zorgen dat het proefschrift drukklaar werd. Dit heeft mij heel veel stress bespaard.

Feikje en Petra, ik vind het super leuk dat jullie mijn paranimfen willen zijn. Feikje, bij jou op de kamer achterin op de 4e verdieping kon ik altijd binnenlopen voor een vraag, goede raad of een gezellig praatje. Petra, door onze gezellige uitjes naar het wijnfestival in de Der Aa-kerk, wintersport in Gerlos, kerstmarkt in Münster, en de ontelbare spelletjes avonden en wandelingen was het een stuk leuker om de volgende dag weer verder te werken aan mijn

proefschrift. Lieve Feikje en Petra, ik ben ontzettend blij dat jullie aan mijn zijde staan tijdens de verdediging van mijn proefschrift.

Lieve (schoon) familie, ik ben de eerste in de familie die gaat promoveren. Een promotietraject was soms een beetje een ver van jullie bed-show, toch luisterden jullie altijd belangstellend naar al mijn verhalen. Ik hoop dat jullie allemaal trots zijn op mij, de eerste dr. in de familie. Douwe en Ria, bedankt dat jullie met veel enthousiasme hebben geholpen met het controleren van de drukproeven. Lieve mam en pap, ik kan jullie niet genoeg bedanken voor alles wat jullie me hebben geleerd en gegeven. Jullie staan altijd klaar met een luisterend oor op de momenten dat ik het nodig heb.

Lieve Pepijn, na al deze bedankjes gaat toch wel het grootste dankwoord naar jou. Je geduld, je luisterend oor, het meedenken, het helpen met de figuren, het lief zijn, het koken, het afleiden en het blijven motiveren. Ik heb het je niet altijd makkelijk gemaakt, maar je was er altijd voor mij. Veel weekenden hebben we samen gewerkt, thuis of bij jou op kantoor, op het eind zelfs beide aan mijn proefschrift, jij de lay-out en de cover en ik de inhoud. Gelukkig was er ook tijd voor ontspanning en hebben we samen oneindig veel kilometers op de racefiets gemaakt. Jouw hulp bij dit proefschrift was onmisbaar. Oneindig veel dank en liefde voor jou.

Dit was hem dan, nu ben ik echt klaar met deze shit.

Liefs Jojanneke

About the author

Jojanneke van Summeren was born on May 20th 1989 in Grubbenvorst, the Netherlands. She graduated from pre-university education at Blariacum college in Blerick in 2007. She then started studying Human Movement Sciences at the University of Groningen, where she received her Master of Science degree in August 2012. She had chosen the specialization "Rehabilitation and Functional Recovery". She did her master's internship at the Department of Rehabilitation, at the Rheumates@Work project supervised by dr. O.T.H.M Lelieveld, dr. W. Armbrust and G.J.F.J. Bos. Her 2-year research project was focused on the physical activity level of children and adolescents. First, she examined in a literature review the relative contribution of nature and nurture on physical activity levels in children and adolescents. Secondly, she investigated the intra-individual variation in physical activity level and pattern of children with juvenile idiopathic arthritis. From 2010 till 2013, she had a job as a research assistant at the Department of Human Movement Sciences, where she administered various motor, physical and cognitive tests to elementary school children, for several research projects.

From May 2013 till October 2014 she worked as a junior researcher at the Department of General Practice at the University Medical Center Groningen (UMCG). Her project was focused on the use of the Outcome Prioritization Tool, a tool for medication review in elderly patients with multimorbidity and polypharmacy. The project was supervised by Prof. dr. F.M. Haaijer-Ruskamp and dr. J. Schuling. For this research she was awarded the poster prize during the EuroDURG conference in 2014.

From February 2014 till February 2019 she performed her PhD research at the same department, under supervision of Prof. dr. M.Y. Berger, dr. J.H. Dekker, dr. Y. Lisman-van Leeuwen and dr. G.A. Holtman. Notably, in 2017 she received a grant from the PW Boer Foundation for Education and Research in Urology to investigate lower urinary tract symptoms (LUTS) and urinary tract infections (UTI) in children with functional constipation, the results of which are presented in this thesis. She obtained the young investigator award

2018 of the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) and a travel grant from the Netherlands Society for Gastroenterology (NVGE) to attend the ESPGHAN conference in 2019. During her PhD research she followed an individual training program to obtain her registration as epidemiologist B from the Epidemiological Society in the Netherlands.

Since November 2019, she works as a postdoctoral researcher at the Netherlands Institute for Health Service Research (Nivel) in Utrecht. Her research projects are focused on the epidemiology and disease burden of respiratory infectious diseases. She is the international study coordinator of the RSV ComNet project. In this project the disease burden of respiratory syncytial virus (RSV) infection in young children in primary care has been investigated in five European countries. She is also invited as a guest lecturer in the training program for pediatric and plevic physiotherapist who are to become pediatric pelvic physiotherapists (kinderbekkenfysiotherapeut).

She lives in Groningen, the Netherlands together with Pepijn Koning.

List of publications

Research Institute SHARE

List of publications

This thesis

1. **van Summeren JJGT**, Holtman GA, Lisman-van Leeuwen Y, van Ulsen-Rust AHC, Vermeulen KM, Tabbers MM, Kollen BJ, Dekker JH, Berger MY. Cost-effectiveness of physiotherapy in childhood functional constipation: a randomized controlled trial in primary care. Family Practice. 2022; epub ahead of print.
2. **van Summeren J**, Holtman GA, Kollen BJ, Lisman-van Leeuwen Y, van Ulsen-Rust AHC, Tabbers MM, Dekker JH, Berger MY. Physiotherapy for Children with Functional Constipation: A Pragmatic Randomized Controlled Trial in Primary Care. The Journal of pediatrics. 2020;216:25-31.e2.
3. **Van Summeren JJ**, Holtman GA, Dekker JH, Berger MY. Quality of life in children with functional constipation: Are child self-reports and parent proxy-reports interchangeable? The Journal of pediatrics. 2020;217:216.
4. **van Summeren JJGT**, Holtman GA, Lisman-van Leeuwen Y, Louer LEAM, van Ulsen-Rust AH, Vermeulen KM, Kollen BJ, Dekker JH, Berger MY. Physiotherapy plus conventional treatment versus conventional treatment only in the treatment of functional constipation in children: Design of a randomized controlled trial and cost-effectiveness study in primary care. BMC pediatrics. 2018;18(1):249.
5. **van Summeren JJGT**, Klunder JW, Holtman GA, Kollen BJ, Berger MY, Dekker JH. Parent-child agreement on health related quality of life in children with functional constipation in primary care. J Pediatr Gastroenterol Nutr. 2018 Dec;67(6)726-731.
6. **van Summeren JJGT**, Holtman GA, van Ommeren SC, Kollen BJ, Dekker JH, Berger MY Bladder symptoms in children with functional constipation: a systematic review J Pediatric Gastroenterol Nutr.2018: 67(5):552-560.
7. **van Summeren J**, Dekker J, Berger M. Pelvic physiotherapy in children with functional constipation: Promising but more research needed. Gastroenterology. 2017;152(8):2080-2081.

Other international publications

8. Hoang U, Button E, Armstrong M, Okusi C, Ellis J, Zambon M, Anand S, Delanerolle G, Hobbs R, **van Summeren J**, Paget J, de Lusignan S. Assessing the clinical and socio-economic burden of RSV in children under 5 years in primary care: Protocol for a prospective cohort study in England and report on adaptations of the study to the COVID-19 pandemic. JMIR Preprints. 2022 doi: 10.2196/preprints.38026.
9. **van Summeren J**, Meijer A, Aspelund G, Casalegno JS, Erna G, Hoang U, Lina B; VRS study group in Lyon, de Lusignan S, Teirlinck AC, Thors V, Paget J. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? Euro Surveill. 2021 Jul;26(29):2100639. doi: 10.2807/1560-7917.ES.2021.26.29.2100639. Erratum in: Euro Surveill. 2021 Jul;26(30).
10. **van Summeren JJGT**, Rizzo C, Hooiveld M, Korevaar JC, Hendriksen JMT, Dückers MLA, Loconsole D, Chironna M, Bangert M, Demont C, Meijer A, Caini S, Pandolfi E, Paget J. Evaluation of a standardised protocol to measure the disease burden of respiratory syncytial virus infection in young children in primary care. BMC Infect Dis. 2021 Jul 26;21(1):705.
11. Staadegaard L, Caini S, Wangchuk S, Thapa B, de Almeida WAF, de Carvalho FC, Fasce RA, Bustos P, Kyncl J, Novakova L, Caicedo AB, de Mora Coloma DJ, Meijer A, Hooiveld M, Huang QS, Wood T, Guiomar R, Rodrigues AP, Lee VJM, Ang LW, Cohen C, Moyes J, Larrauri A, Delgado-Sanz C, Demont C, Bangert M, Dückers M, **van Summeren J**, Paget J. Defining the seasonality of respiratory syncytial virus around the world: National and subnational surveillance data from 12 countries. Influenza Other Respir Viruses. 2021 Nov;15(6):732-741.
12. Staadegaard L, Caini S, Wangchuk S, Thapa B, Ferreira de Almeida WA, Cotrim de Carvalho F, Njouom R, Fasceμ RA, Bustos P, Kyncl J, Novakova L, Caicedo AB, de Mora Coloma, Meijer A, Hooiveld M, Huang S, Wood T, Guiomar R, Rodrigues AP, Danilenko D, Stolyarov K, Ming Lee VJ, Wei Ang L, Cohen C, Moyes J, Larrauri A, Delgado-Sanz C, Quynh Le M, Hoang PVM, Demont C, Bangert M, **van Summeren J**, Dückers M, Paget J. The global epidemiology of RSV in community and hospitalized care: findings from 15 countries. Open Forum Infectious Diseases. 2021 Mar 30;8(7).
13. Staadegaard L, Meijer A, Rodrigues AP, Huang S, Cohen C, Demont C, **van Summeren J**, Caini S, Paget J. Temporal Variations in Respiratory Syncytial Virus Epidemics, by Virus Subtype, 4 Countries. Emerg Infect Dis. 2021 May;27(5):1537-1540.

14. Rizzo C, Loconsole D, Pandolfi E, Ciofi Degli Atti ML, **van Summeren J**, Paget J, Russo L, Campagna I, Croci I, Gesualdo F, Concato C, Linardos G, Bartolucci V, Ciampini S, Muda AO, Raponi M, Chironna M. Sars-Cov2 Not Detected in a Pediatric Population With Acute Respiratory Infection in Primary Care in Central and Southern Italy From November 2019 to Early March 2020. Front Pediatr. 2021 May 11;9:620598.
15. Te Brummelstroete GH, Loohuis AM, Wessels NJ, Westers HC, **van Summeren JJ**, Blanker MH. Scientific evidence for pelvic floor devices presented at conferences: An overview. Neurourology and urodynamics. 2019;38(7):1958-65.
16. **van Summeren JJ**, Schuling J, Haaijer-Ruskamp FM, Denig P. Outcome prioritisation tool for medication review in older patients with multimorbidity: A pilot study in general practice. Br J Gen Pract. 2017; 67(606). doi: 10.3399/bjgp17X690485.
17. **Summeren JJ**, Haaijer-Ruskamp FM, Schuling J. Eliciting preferences of multimorbid elderly adults in family practice using an outcome prioritization tool. J Am Geriatr Soc. 2016;64(11).

National publications

1. **van Summeren JJGT**, Hendriksen JMT, Paget J, Meijer A. Weinig RS-virus afgelopen winter; hoe komt dit en wat zijn de verwachtingen voor de komende seizoenen? Tijdschrift infectieziekten 2021;16(3):80-5.
2. Holtman G, **van Summeren J**. Probiotica tegen diarree bij antibiotica. Huisarts en wetenschap, feb 2019.
3. **van Summeren J**, Holtman G. Dieet voor kinderen met functionele buikpijn. Huisarts en wetenschap. 2018;61:75-75.

Research Institute SHARE

This thesis is published within the Research Institute SHARE (Science in Healthy Ageing and healthcaRE) of the University Medical Center Groningen / University of Groningen.
Further information regarding the institute and its research can be obtained from our internet site: https://umcgresearch.org/w/share

More recent theses can be found in the list below.
(supervisors are between brackets)

Helmich MA
What's in a mood?; looking for dynamic predictors of individual improvemenet in de depression
(prof M Wichers, prof AJ Oldehinkel, dr E Snippe, dr LF Brinkmann)

Kouwenhove L van
On the design of rocker profile shoes
(dr JM Hijmans, prof GJ Verkerke, prof R Dekker)

Niccodemi G
Skills, early-life environment and health in adulthood
(prof RJM Alessie, prof V Angelini, dr GE Bijwaard)

Wang J
Breast cancer screening in Europe and China; strategy evaluation and optimization
(prof GH de Bock, prof W Lu, dr MJW Greuter)

Zanden V van der
Studies on perioperative care for frail patients; focused on gynecology
(prof BC van Munster, prof MJE Mourits, dr KM Paarlberg, dr WJ Meijer)

Damsma-Bakker A
Speaking of what matters most; the spirituality and the spiritual needs of Dutch children with a chronic condition
(prof PF Roodbol, dr R van Leeuwen)

2021

Ontiri SK
Improving access to quality family planning services in Kenya by addressing contracepive discontinuation
(prof J Stekelenburg, dr R Biesma-Blanco, dr M Kabue)

Acevedo Mesa MA
Beyond a symptom count: Addressing the difficulties of measuring Functional Somatic Symptoms
(prof J Rosmalen, dr R Tendeiro-Monden, dr JN Tendeiro, dr AM Roest)

Flikweert ER
Proximal femoral fractures: influence of multidisciplinary care
(prof RL Diercks, dr M Stevens, dr KW Wendt, dr GJ Izaks)

Hulshof TA
Quantitative appraisal of trial methods in reviews: an investigation of antipsychotic drug effects in dementia
(prof SU Zuidema, dr HJ Luijendijk)

Broekstra R
Values of trust and participation in scientific data repositories
(prof RP Stolk, prof S Otten, dr ELM Maeckelberghe, dr JL Aris-Meijer)

Du Y
CT lung cancer screening in China; the necessity to optimize target population
(prof GH de Bock, prof M Oudkerk, dr GA Sidorenkov)

Gol JM
Betwixt and between; medical care for functional somatic symptoms
(prof JGM Rosmalen, prof ROB Gans, prof RC Oude Voshaar)

For earlier theses visit our website

Research Institute
SHARE