Physiotherapy for Children with Functional Constipation

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

Published in:
The Journal of Pediatrics

DOI:
10.1016/j.jpeds.2019.09.048

Publication date:
2020

physiotherapy for children with functional constipation

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

Published in:
The Journal of Pediatrics

Physiotherapy for children with functional constipation: A pragmatic randomized controlled trial in primary care

Jojanneke JGT van Summeren MSc[1], Gea A Holtman PhD[2], Boudewijn J Kollen PhD[3], Yvonne Lisman-van Leeuwen PhD[4], Alice HC van Ulsen-Rust,[5] Merit M Tabbers MD PhD[6], Janny H Dekker MD PhD[7], Marjolein Y Berger, MD PhD[8]

Affiliations:

[1] j.j.g.t.van.summeren@umcg.nl, University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands

[2] g.a.holtman@umcg.nl, University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands

[3] b.j.kollen@umcg.nl, University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands

[4] y.lisman-van.leeuwen@umcg.nl University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands

[5] alicevanulsen@hotmail.com, Paediatric Pelvic physiotherapy, Pelvicum kinderbekkenfysiotherapie, Groningen, the Netherlands,

[6] m.m.tabbers@amc.uva.nl, Emma Children's Hospital/Amsterdam UMC - location AMC, Amsterdam, Department of Pediatric Gastroenterology and Nutrition, the Netherlands.

[7] j.h.dekker@umcg.nl, University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands

[8] m.y.berger@umcg.nl, University of Groningen, University Medical Center Groningen, Department of General Practice and Elderly care medicine, the Netherlands (Corresponding author)

Corresponding author: Marjolein Berger,

University of Groningen, University Medical Center Groningen, Department of General practice and Elderly care medicine, PO Box 196, 9700 AD Groningen, The Netherlands, m.y.berger@umcg.nl, Phone number: +31 50 361 6722

Presentations:

This study will be presented on the annual meeting of the European Society for Gastroenterology and Nutrition on 7 June 2019 in Glasgow, United Kingdom and at the Dutch Epidemiology Conference on 13 June 2019 in Groningen, the Netherlands.

Conflict of interest:

The authors have no conflicts of interest disclose.

Funding source

This trial is funded by the Netherlands organization for Health Research and Development (ZonMw), project number 837001409.

Financial disclosure

The funding organization had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Authors' contributions

All authors are responsible for the reported research, have participated in the concept and design, and have approved the submitted manuscript. JVS collected the data. JVS and BK analyzed the data. JVS drafted the initial version of the manuscript. GH, BK, JD, and MB critically reviewed and revised the initial version of the manuscript. YLvL, AUR, and MT critically reviewed the final version of the manuscript.

Short title: Physiotherapy for childhood functional constipation

Word count: 2976

Number of tables: 2

Number of figures: 1

Online only: 3 tables

Key words: Primary care, children, gastroenterology, physiotherapy, functional constipation

Abstract

Objective: To determine the effectiveness of physiotherapy plus conventional treatment (CT) compared to CT alone for the treatment of functional constipation (FC) in children aged 4–17 years in primary care.

Methods: Pragmatic randomized controlled trial with 8 months follow-up. Primary care physicians recruited children diagnosed with FC (n=234), and pediatricians recruited newly referred children with a diagnosis of FC (n=11). CT 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 FC (Rome III criteria) without laxative use. Secondary outcomes included the absence of FC irrespective of continuation of laxative use and global perceived treatment effect.

Results: Children were allocated to CT plus physiotherapy or CT 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 CT (aRR 0.80, 95%CI 0.44–1.30). At 4 months, fewer children receiving physiotherapy had treatment success (17%) than children receiving CT alone (28%), but this had equalized by 8 months (42% and 41%, respectively). The percentage of children without FC, 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 CT (aRR 1.40; 95%CI 1.00–1.73).

Conclusions: We find no evidence to recommend physiotherapy for all children with FC in primary care.

Trial registration: Netherlands Trial Register (NTR4797), registered 8 September 2014.

Abbreviations: CT, conventional treatment; FC, functional constipation; PCP, primary care physician; RR, relative risk; aRR, adjusted relative risk; CI, confidence interval; RCT, randomized controlled trial; QPGS-RIII, Questionnaire on Pediatric Gastrointestinal Symptoms Rome III; OR, odds ratio;

Background

Childhood functional constipation (FC) 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 FC 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.[4-7] At present, the management of FC 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, 10-12] 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 FC have persistent symptoms after 6–12 months of conventional treatment (CT) 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 FC 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.[16-19] Two small randomized controlled trials 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 FC 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 randomized controlled trial (RCT), we aimed to determine the effectiveness of physiotherapy plus CT compared to CT alone over 8-month follow-up period for the treatment of FC in children aged 4–17 years in primary care in the Netherlands.

Methods

Design

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 when aged ≥12 years, provided written informed consent.

Participants

Children aged 4–17 years diagnosed with FC 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 FC (incident cases PCP), while general pediatricians from five outpatient departments in the north of the Netherlands recruited consecutive children who were newly referred with a diagnosis of FC (incident cases pediatrician) (Figure 1). Any child who had consulted a PCP for FC in the preceding 12 months also received a leaflet explaining the study, plus a short questionnaire to assess eligibility (e.g., presence of FC symptoms or laxative use in the preceding 4 weeks) (prevalent cases PCP). We excluded children with psychopathology that 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 ratio to one of two 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 CT only, which involved education, dietary advice, toilet training, and laxative prescribing according to Dutch guidelines for the management of FC.[27] These are comparable to international guidelines.[8] No restrictions or specific instructions were given to physicians regarding CT.

Children in the intervention group received CT plus physiotherapy that was carried out by specialist physiotherapists (i.e., 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 six 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 nine 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 one of the six Rome III criteria, with no laxative use for 4 weeks before measurement (absence of FC without laxative use).[28] Rome III criteria were assessed with the standardized Questionnaire on Pediatric Gastrointestinal Symptoms Rome III (QPGS-RIII), 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 aged 4–12 years) or children themselves (if aged 13–17 years). In all cases, parents answered the question "Did your child use laxatives in the past four 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. 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 to 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 (Centre for Multilevel Modelling, University of Bristol, UK). 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 two-sided P-value of <0.05. 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 ($p<0.1$) (Table S3).

Results

Participants

Figure 1 summarizes the participant flow for 134 children randomly assigned to the study groups. Among all recruiting physicians, 71 GPs and pediatricians in 3 district hospitals actually included at least one 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 to those of completers. In the CT group, 6 children were referred to a physiotherapist due to 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 (interquartile range 63–145 days) between the first and last sessions.

Intention-to-treat analyses

In total, 115 participants completed at least one of the two 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 FC and no laxative use) were not significantly different between intervention and control group (aRR 0.80, 95%CI 0.44–1.30). At 4 months, fewer children receiving physiotherapy (17%) had treatment success than children receiving CT alone (28%), but this had equalized by 8 months (42% and 41%).

When treatment success was defined as absence of FC 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, while 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 CT (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).

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 FC 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 (online) shows the baseline characteristics of the subgroups of children with (n = 72) and without (n = 43) chronic laxative use. Table 4 (online) 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 FC 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.

Prognostic factors for treatment success after 8 months

Stool withholding, fecal incontinence and abdominal pain were in the univariate analyses, negatively associated ($p < 0.1$) with treatment success of FC after 8 months (Table 5; online).

Discussion

During the study period, we found no benefit from adding physiotherapy to CT 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 CT 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 FC was previously measured in two studies in district (n = 53)[20] and university (n = 72)[21] hospitals. Neither study defined treatment success as the absence of FC without laxative use, but one did evaluate the effectiveness of physiotherapy as the absence of FC irrespective of laxative use.[20] Defined in this way, the treatment success rate in the CT 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 CT 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 to 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 CT groups (OR 2.7, 95%CI 1.0 to 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 to those used in our study.[21]

Outcomes in clinical trials of children with FC have varied greatly.[40] 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 FC.[41] 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 FC,[41] but we only used a 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 FC, 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,[39] 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.

Implications for clinicians and researchers

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

Conclusions

In conclusion, we found no objective benefit from adding physiotherapy to CT for the whole group of children with FC 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.

Acknowledgments

We would like to thank the primary care physicians and general pediatricians for recruiting and treating the children in this study. We would also like to thank the physiotherapists who helped to develop the physiotherapy program and those who performed the interventions. Editorial assistance was provided by Dr. Robert Sykes (www.doctored.org.uk). Last, but not least, we are grateful to all participating children and their parents for their invaluable contributions.

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;198:121-130.

2 Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best practice & research Clinical gastroenterology* 2011;25:3-18.

3 Rajindrajith S, Devanarayana NM, Perera BJC, Benninga MA. Childhood constipation as an emerging public health problem. *World Journal of Gastroenterology* 2016;22:6864.

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;166:1482-1487.

5 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;31:938-49.

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;163:1069-1072.

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 doi:10.1097/MPG.0000000000000266 [doi].

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 doi:10.1136/adc.2007.127233 [doi].

10 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.

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;199:132-139.

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. *Neurogastroenterology & 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.e1-4.

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 M L, 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. *The Cochrane Library* 2016.

19 Gutiérrez C, Marco A, Nogales A, Tebar R. Total and segmental colonic transit time and anorectal manometry in children with chronic idiopathic constipation. *J Pediatr Gastroenterol Nutr* 2002;35:31-8.

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 Disease* 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 pediatrics* 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.

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;150:1456,1468. 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;154:749,753. 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 doi:10.1097/MPG.0000000000000527 [doi].

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;63:760,766. 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. *Journal of general internal medicine* 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 Hernán MA, Robins JM. Per-protocol analyses of pragmatic trials. *N Engl J Med Overseas Ed* 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 Paediatrics Open* 2017;1.

39 van Ginkel R, Reitsma JB, Büller HA, Taminiau JA, Benninga MA. Childhood constipation: longitudinal follow-up beyond puberty. *Gastroenterology* 2003;125:357-63.

40 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.

41 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.

Figures legends

Figure 1. Flowchart of participant recruitment and participant flow through the study.

Abbreviations: FC, functional constipation; PCP, Primary Care Physician. 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).

[a] In the physio group the number of analyzed children in the per protocol analysis at 4 months was 56 because three children did not receive physiotherapy and were lost to follow-up.

[b] In the conventional treatment group the number of analyzed children in the per protocol analysis at 8 months follow-up was 44 because two children did receive physiotherapy after 4 months and were lost to follow-up at 8 months.

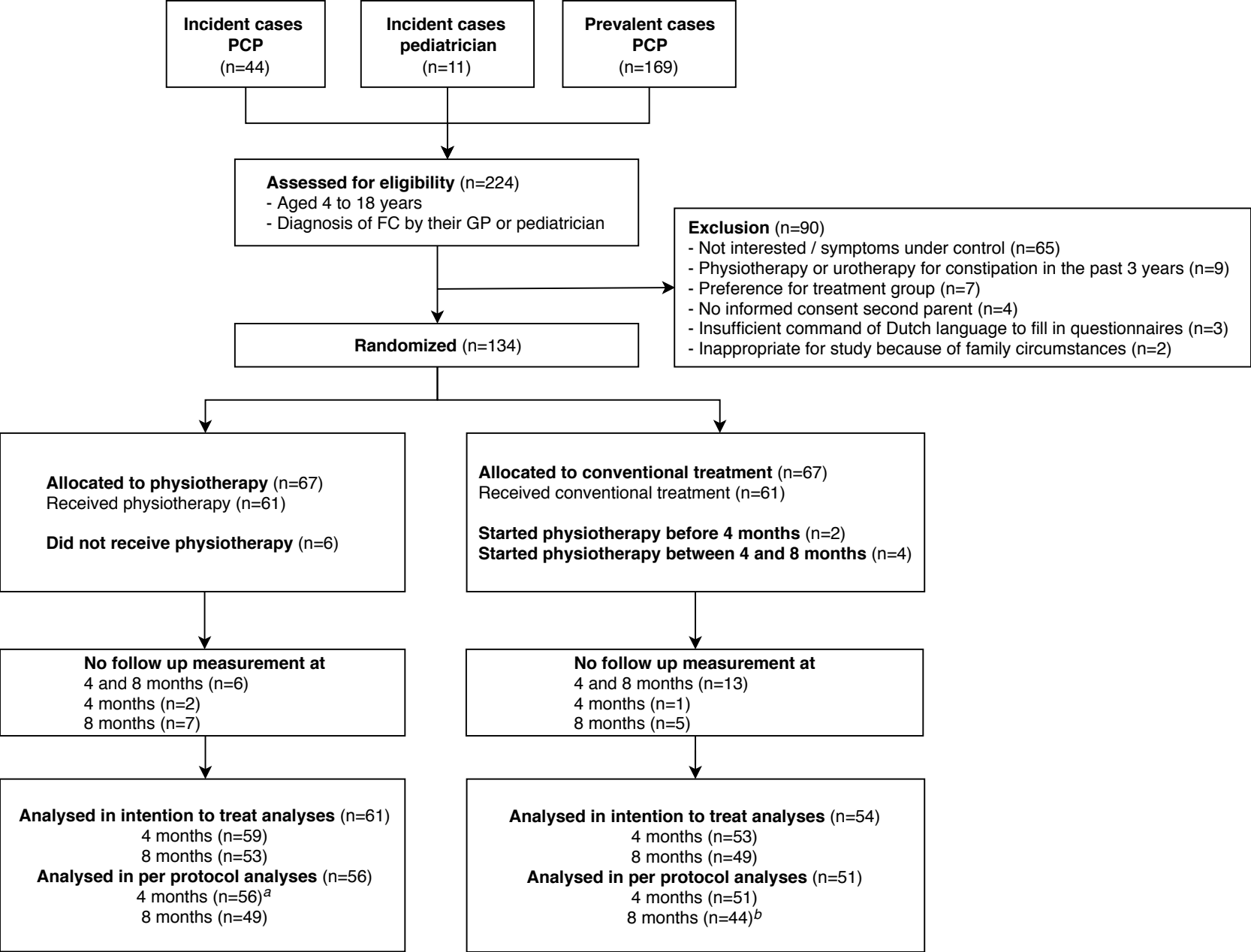
Incident cases PCP (n=44)
Incident cases pediatrician (n=11)
Prevalent cases PCP (n=169)
Assessed for eligibility (n=224)
- Aged 4 to 18 years
- Diagnosis of FC by their GP or pediatrician
Exclusion (n=90)
- Not interested / symptoms under control (n=65)
- Physiotherapy or urotherapy for constipation in the past 3 years (n=9)
- Preference for treatment group (n=7)
- No informed consent second parent (n=4)
- Insufficient command of Dutch language to fill in questionnaires (n=3)
- Inappropriate for study because of family circumstances (n=2)
Randomized (n=134)
Allocated to physiotherapy (n=67)
Received physiotherapy (n=61)
Did not receive physiotherapy (n=6)
Allocated to conventional treatment (n=67)
Received conventional treatment (n=61)
Started physiotherapy before 4 months (n=2)
Started physiotherapy between 4 and 8 months (n=4)
No follow up measurement at
4 and 8 months (n=6)
4 months (n=2)
8 months (n=7)
No follow up measurement at
4 and 8 months (n=13)
4 months (n=1)
8 months (n=5)
Analysed in intention to treat analyses (n=61)
4 months (n=59)
8 months (n=53)
Analysed in per protocol analyses (n=56)
4 months (n=56)a
8 months (n=49)
Analysed in intention to treat analyses (n=54)
4 months (n=53)
8 months (n=49)
Analysed in per protocol analyses (n=51)
4 months (n=51)
8 months (n=44)b

Table 1. Baseline characteristics (n = 134)

	Physio (n = 67)	CT (n = 67)
Age (years), mean ± standard deviation	7.3 ± 3.4	7.8 ± 3.5
Girls n (%)	38/67 (57%)	44/67 (66%)
Duration of symptoms n (%)		
≤3 months	4/58 (7%)	12/62 (19%)
3–12 months	6/58 (10%)	10/62 (16%)
>12 months	48/58 (83%)	40/62 (65%)
Chronic laxative use [a] n (%)	41/57 (72%)	31/58 (53%)
Previous episodes of FC 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 weeks n (%)	46/56 (82%)	44/59 (75%)
Abdominal pain/discomfort ≥ once a week n (%)	35/66 (53%)	41/67 (61%)
Constipation-related symptoms and signs (Rome III criteria)		
≤2 defecations in the toilet per week n (%)	16/67 (24%)	10/67 (15%)
Fecal incontinence ≥1 per week 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%)

Abbreviations: CT, conventional treatment; FC, functional constipation; Physio, physiotherapy.

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

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

	4 months		8 months				
	Physio	**CT**	**Physio**	**CT**	**RR /β (95%CI)**	**aRR/β (95%CI)[a]**	**p**
Total group, N	59	53	53	49			
Absence of FC, 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)	0.397
Absence of FC, 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)	0.405
Quality of life *median (IQR)*	82 (75–88)	84 (74–88)	85 (79–92)	85 (77–90)	β: 0.1 (-4.0 to 4.3)	β **:** -0.9 (-5.2 to 3.4)	0.675
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)**	**0.048***

Abbreviations: (a)RR, (adjusted) relative risk; β, beta coefficient; CT, conventional treatment; Physio, physiotherapy.

[a] Adjusted for chronic laxative use. * $p < 0.05$

Table S1. Baseline characteristics of children with and without chronic laxative use

	Children with chronic laxative use (n = 72) [a]		Children without chronic laxative use (n = 43) [a]	
	Physio (n = 41)	**CT (n = 31)**	**Physio (n = 16)**	**CT (n = 27)**
Age (in years) 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 weeks n (%)	35/41 (85%)	26/31 (84%)	11/15 (69%)	17/27 (63%)
Abdominal pain/discomfort ≥ once a week 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 per week n (%)	8/41 (20%)	3/31 (10%)	5/16 (31%)	5/27 (19%)
Fecal incontinence ≥1 per week 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%)

Abbreviations: CT, conventional treatment; Physio, physiotherapy.

[a] chronic laxative use was not known for 19 children.

Table S2. 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			
	Physio	**CT**	**Physio**	**CT**	**RR or β (95%CI)**	**p**
Children with chronic laxative use	N = 39	N = 26	n = 31	n = 21		
Absence of FC without the use of laxatives n (%)	8/39 (21%)	6/26 (23%)	15/31 (48%)	8/21 (38%)	1.01 (0.52–1.90)	0.783
Absence of FC with or without laxatives n (%)	28/38 (74%)	16/26 (62%)	25/30 (83%)	10/21 (48%)	**1.40* (1.00–1.63)**	**0.049**
Quality of life *median* (*IQR)*	82 (76–88)	87 (77–92)	87 (81–92)	88 (82–92)	β: 0.5 (-4.7 to 5.7)	0.850
Global perceived effect n (%)	23/39 (59%)	8/25 (32%)	19/31 (61%)	10/20 (50%)	1.51 (0.96–1.96)	0.069
Children without chronic laxative use	N = 14	N = 18	N = 15	N = 19		
Absence of FC without the use of laxatives n (%)	1/14 (7%)	7/18 (39%)	5/15 (33%)	10/19 (53%)	0.46 (0.15–1.04)	0.066
Absence of FC irrespective laxative use n (%)	7/14 (50%)	13/18 (72%)	9/15 (60%)	14/19 (74%)	0.77 (0.35–1.12)	0.259
Quality of life *median, (IQR)*	78 (63–87)	83 (68–87)	80 (63–86)	82 (69–88)	β: -3.5 (-11.1 to 4.2)	0.374
Global perceived effect n (%)	8/13 (62%)	9/18 (50%)	10/15 (67%)	10/19 (53%)	1.25 (0.69–1.67)	0.382

Abbreviations: β, beta coefficient; CT, conventional treatment; Physio, physiotherapy; RR, relative risk.

* $p < 0.05$

Table S3. Distribution of candidate predictors in relation to two definitions of treatment success in the whole study population after 8 months (results of univariate logistic regression analyses).

	Model 1 Absence of FC and no laxatives (n=42)	Presence of FC or the use of laxatives (n=59)	Odds ratio (95%CI)	P	R^2 (Nagelkerke)	*Model 2* Absence of FC (n=68)	Presence of FC (n=33)	Odds ratio (95%CI)	P	R^2 (Nagelkerke)
Abdominal pain, ≥1 weekly (n, %)	19/42 (45)	37/59 (62)	0.5 (0.2-1.1)	0.083	0.040	32/68 (47)	24/33 (73)	0.3 (0.1-0.8)	0.017	0.082
Defecation frequency ≤2 weekly (n,%)	0/42 (0)	6/59 (10)	0.8 (0.3-2.5)	0.718	0.002	0/68 (0)	6/33 (18)	1.1 (0.3-3.4)	0.895	0.000
Fecal incontinence, ≥1 weekly (n,%)	1/42 (2)	24/59 (41)	0.5 (0.2-1.1)	0.082	0.041	4/68 (6)	21/33 (64)	0.2 (0.1-0.5)	0.000	0.178
Painful or hard bowel movements (n,%)	8/42 (19)	29/59 (49)	0.9 (0.4-2.2)	0.872	0.000	13/68 (19)	24/33 (73)	0.5 (0.2-1.3)	0.141	0.032
Stool withholding (n,%)	0/42 (0)	15/59 (25)	0.3 (0.1-0.8)	0.012	0.090	1/68 (1)	14/33 (42)	0.2 (0.1-0.4)	0.000	0.207
Large stools that obstruct the toilet (n,%)	1/42 (2)	9/59 (15)	0.7 (0.2-2.2)	0.565	0.004	3/68 (4)	7/33 (21)	0.9 (0.3-2.6)	0.801	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.

[b] The candidate predictor chronic laxative use has 16 missing values.