From Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

GUTS OVER FEAR - INTERNET THERAPY FOR ABDOMINAL PAIN IN CHILDREN

Maria Lalouni

Stockholm 2018

GUTS OVER FEAR

Internet therapy for abdominal pain in children

THESIS FOR DOCTORAL DEGREE (Ph.D.)

To be defended in public at the CMB Lecture Hall, Karolinska Institutet, Stockholm, Sweden

Friday 15th of June 2018 at 9 am

By

Maria Lalouni

Principal Supervisor:
MD PhD Ola Olén
Karolinska Institutet
Department of Medicine, Solna
Clinical Epidemiology Unit

Co-supervisors:
Associate Professor Brjánn Ljótsson
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Associate Professor Eva Serlachius
Karolinska Institutet
Department of Clinical Neuroscience
Center for Psychiatric Research

Associate Professor Erik Hedman-Lagerlöf
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Opponent:
Professor Tonya Palermo
University of Washington
Department of Anesthesiology and Pain Medicine
&
Department of Pediatrics

Examination Board:
Professor Maria Tillfors
Karlstad University
Department of Social and Psychological studies
Division of Psychology

Associate Professor Torbjörn Lind
Umeå University
Department of Clinical Sciences
Unit of Pediatrics

Associate Professor Jonas Ramnerö
Stockholm University
Department of Psychology
Division of Clinical Psychology

To Estrid, Dante and Jalal!

ABSTRACT

Background: Pediatric functional abdominal pain disorders (FAPDs) are prevalent and associated with painful symptoms, low quality of life, and functional impairments. The origin is likely multifactorial and includes psychological factors (e.g., anxiety and coping mechanisms), biological factors (e.g., visceral sensitivity and gut microbiota), and social factors (e.g., interaction with parents or teachers). There is limited support for dietary and pharmacological treatments in FAPDs, but support for the effectiveness of cognitive behavioral therapy (CBT) is growing.

Aims: The overall aim of the thesis was to develop and evaluate a therapist-supported exposure-based CBT for children 8-12 years with FAPDs, which could, if proven effective, increase accessibility of treatments for children with FAPDs. The specific aims were to:

- Assess feasibility, acceptability, and potential effectiveness of the preliminary protocol of exposure-based CBT in a face-to-face setting (Study I).

- Assess feasibility, acceptability, and potential effectiveness of the exposure-based CBT converted to an internet platform (Internet-CBT, Study II).

- Evaluate effectiveness and cost effectiveness of the Internet-CBT compared with treatment as usual (Study III).

- Investigate if gastrointestinal-specific anxiety and avoidance behaviors mediated a change in gastrointestinal symptoms in Internet-CBT compared with treatment as usual and if baseline values of the proposed mediators moderated the mediation (Study IV).

Methods: All participants were children 8-12 years with FAPDs referred to the studies by their physicians. Treatment consisted of therapist-supported exposure-based CBT, delivered face-to-face (Study I) or online (studies II-IV) along with parental sessions or modules. All measures were self-assessed by children and parents. Primary outcome was pain intensity (Study I) and gastrointestinal symptoms (Study II-IV). Secondary outcomes included quality of life, school absence, anxiety, and parental responses to their children´s symptoms (Studies I-III), cost effectiveness and parental catastrophizing (Study III), gastrointestinal-specific anxiety (Study II-IV), and avoidance behavior (Study I-IV). Statistical analyses used to test within- and between-group effects were t-tests (Study I) and multi-level linear mixed models (Study II and III). Differences in costs between groups were assessed with generalized linear models (Study III). Univariate and multivariate growth models were used to assess mediation and moderated mediation (Study IV).

Results: Therapist-supported exposure-based CBT, delivered face-to-face or online, rendered high adherence and treatment completion (Study I-III). Participating children and parents were satisfied with the treatment and perceived it to be helpful in dealing with abdominal symptoms (Study I-III). There were significant treatment effects in gastrointestinal symptoms, quality of life, gastrointestinal-specific anxiety, avoidance behavior, anxiety,

parental catastrophizing, and parental responses to their child's symptoms for Internet-CBT when compared with treatment as usual (Study III). Internet-CBT was found to be cost effective and even cost saving compared with treatment as usual (Study III). A reduction in gastrointestinal-specific anxiety and avoidance behavior mediated a reduction in gastrointestinal symptoms for children receiving Internet-CBT compared with children receiving treatment as usual (Study IV). Baseline values of gastrointestinal specific-anxiety and avoidance behavior moderated the mediation (Study IV).

Conclusions: Internet-CBT based on exposure exercises and parental support for children with FAPDs is feasible, acceptable, clinically effective, and cost effective compared with treatment as usual. Gastrointestinal-specific anxiety and avoidance behavior are potential mechanisms of change in exposure-based Internet-CBT compared with treatment as usual. Internet-CBT seems to be particularly effective for children with high levels of gastrointestinal-specific anxiety and avoidance behaviors. The treatment has the potential to increase the availability of evidence-based treatments a large group of children with FAPDs.

LIST OF SCIENTIFIC PAPERS

I. Lalouni M, Olén O, Bonnert M, Hedman E, Serlachius E, Ljótsson B. Exposure-Based Cognitive Behavior Therapy for Children with Abdominal Pain: A Pilot Trial. Choonara I, editor. PLoS ONE. 2016;11(10):e0164647.

II. Lalouni M, Ljótsson B, Bonnert M, Hedman-Lagerlöf E, Högström J, Serlachius E, Olén O. Internet-Delivered Cognitive Behavioral Therapy for Children With Pain-Related Functional Gastrointestinal Disorders: Feasibility Study. JMIR Ment Health. 2017 Aug 10;4(3):e32.

III. Lalouni M, Bonnert M, Ssegonja R, Benninga MA, Bjureberg J, Högström J, Sahlin H, Simrén M, Feldman I, Hedman-Lagerlöf E, Serlachius E, Olén O. Effectiveness and cost-effectiveness of cognitive behavioural therapy via internet for children with functional abdominal pain disorders: a randomized controlled trial. (Manuscript).

IV. Lalouni M, Hesser H, Bonnert M, Hedman-Lagerlöf E, Serlachius E, Olén O, Ljótsson B. Mediation and moderation of fear and avoidance in cognitive behavioural therapy for children with functional abdominal pain disorders. (Manuscript).

CONTENTS

LIST OF ABBREVIATIONS

FAPDs	Functional abdominal pain disorders
IBS	Irritable bowel syndrome
FD	Functional dyspepsia
FAP-NOS	Functional abdominal pain – not otherwise specified
IBD	Inflammatory bowel disease
CBT	Cognitive behavioral therapy
Internet-CBT	Internet-delivered cognitive behavioral therapy
FODMAP	Fermentable oligo-, di-, and monosaccharides, and polyols
CI	Confidence interval
BIP	The child-internet project
BUP KFE	The child and adolescent psychiatry clinical research unit

1 INTRODUCTION

Imagine abdominal pain so intense you can barely stand up straight. You collapse on the couch and roll up like bowl. Your stomach is swollen like a balloon and you feel nauseous. Then imagine this happening again and again. Your doctor assures you all tests are OK. But what if she is mistaken?

This is the reality for many children. Functional abdominal pain disorders are so prevalent that in every classroom 2-4 children are likely affected. For many children the symptoms lead to impairments in their everyday lives.

Studies in adults suggest that the behavioral response to one's own abdominal symptoms affect how subsequent symptoms are perceived. A strong and forceful reaction confirms the importance of the abdominal symptoms and likely leads to prioritization and amplification of them. In children parental behavior is also a factor. Parents' responses to the child's pain expressions have been shown to influence how symptoms are perceived and managed by the child. In other words, the behaviors of both children and their parents are of great importance in the treatment of pediatric functional abdominal pain disorders.

The treatment developed and evaluated in this thesis was designed to empower children to take back the control of their symptoms and lives. With support from their therapists the children strived hard and to a high extent succeeded in their efforts. The children showed that they and not their stomachs are in charge and that they had attained guts over fear.

Stockholm April 2018

2 BACKGROUND

2.1 FUNCTIONAL ABDOMINAL PAIN DISORDERS (FAPDS)

Long-lasting abdominal pain was first described by British pediatrician John Apley in 1958 as recurrent abdominal pain.[1] In the 1980's researchers united in forming more specific criteria for functional abdominal disorders, the Rome criteria. The Rome III criteria were released in 2006[2] and the Rome IV criteria were released in 2016.[3] Pediatric functional abdominal pain disorders (FAPDs) according to the Rome IV criteria are characterized by abdominal pain or discomfort that *after appropriate medical evaluation cannot be attributed to another medical condition*. FAPDs with pain or discomfort that occur *at least four times a month for at least two months* include irritable bowel syndrome (IBS), functional dyspepsia (FD), and functional abdominal pain-not otherwise specified (FAP-NOS), see Figure 1 for characteristics separating the sub-diagnoses. The first two studies in the thesis used the Rome III criteria[2] and the last two studies used the Rome IV criteria.[3] Two studies assessing the differences between the Rome III and IV criteria concluded that children diagnosed with the Rome IV criteria were more likely to receive a FD or IBS diagnosis compared with children diagnosed with the Rome III criteria. The studies also concluded that there is an increased overlap between IBS and FD in Rome IV compared with Rome III.[4,5]

IBS	FD	FAP-NOS
• Related to defecation and/or • Change in frequency and/or form of stool • Not releaved with laxatives	• Pain or discomfort in upper stomach and/or • Early satiety and/or • Fullness after normal sized meal	• Insufficient criteria for IBS or FD
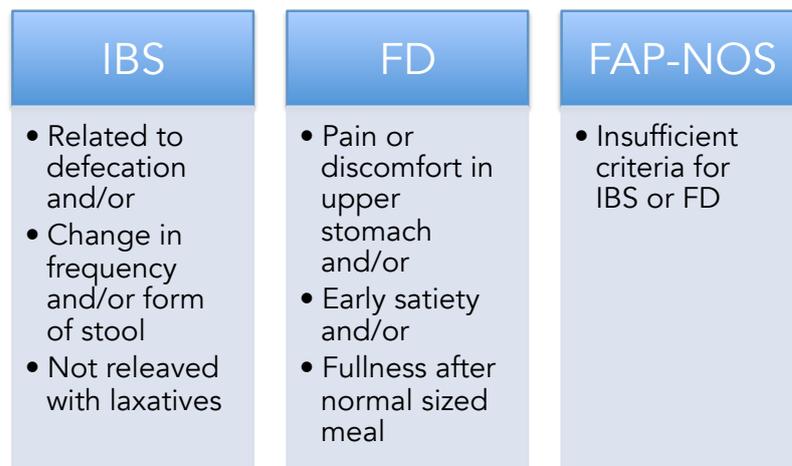
Figure 1. Characteristics separating irritable bowel syndrome (IBS), functional dyspepsia (FD), and functional abdominal pain–not otherwise specified (FAP-NOS) according to the Rome IV criteria[3].

2.2 PREVALENCE AND IMPAIRMENTS ASSOCIATED WITH FAPDS

The prevalence of FAPDs varies between studies, likely because of differences in source population, diagnostic criteria used, and diagnostic procedures. A recent meta-analysis found a worldwide-pooled prevalence of 13.5%,[6] which is comparable to what has been found in Swedish studies.[7,8] The prevalence of FAPDs in girls is 50% higher than in boys.[6] FAPDs are associated with anxiety, depression, school absenteeism, parental work absenteeism,[9] and with anxiety later in adulthood.[10] A study that followed 392 children with FAPDs 5-15 years after their initial assessment showed that 41% of the children still had abdominal problems in adulthood.[11] Another study of children with FAPDs found that two or more of the risk

factors: high baseline levels of pain intensity, functional disability, or anxiety were associated with increased functional disability six months later.[12] Children with FAPDs report lower quality of life than healthy children,[9] with levels comparable to and even lower than children with chronic somatic disorders such as inflammatory bowel disease.[13,14] In Sweden, children with FAPDs account for 11% of all visits in secondary pediatric care and 25-30% of the visits to pediatric gastrointestinal units and abdominal pain is the second most common cause for visiting pediatric emergency services.[15] The combination of high prevalence, associations with school and parental work absenteeism, and large health care consumption render substantial societal costs. The average cost for assessing a child with FAPDs within tertiary care in USA exceeds US$6000[16] and a study from the Netherlands estimated a mean annual cost of US$3122 for a child with FAPDs, including costs from both the healthcare and the societal perspective.[17] There are potentially great gains to be made, both to the individual and to the society, if children with FAPDs were treated in an effective and cost effective way.

2.3   ETIOLOGY AND CONTRIBUTING FACTORS

It is a widely held view that the cause of FAPDs is multifactorial, with biological, social, and psychological factors interacting during development and maintenance of the disorders.[18] An overview of factors shown to contribute to pediatric FAPDs is described below.

2.3.1   Visceral sensitivity and vigilance

A common feature in patients with FAPDs is visceral sensitivity, which refers to a lowered threshold for sensing pain and other symptoms from the gastrointestinal tract. Visceral sensitivity has been shown in both adults[19] and children[20] with IBS. A large study with five cohorts of adult patients with FAPDs showed that symptom severity gradually increased with increased levels of visceral sensitivity.[21] In a study of a psychological treatment for adult IBS, a decrease in visceral sensitivity was found to mediate an improvement in abdominal symptoms.[22] Visceral sensitivity is closely related to vigilance, representing a tendency to pay attention to or to notice abdominal symptoms. If symptoms are perceived as fearful, the vigilance will likely be increased as a means to protect the individual from harm (see The fear and avoidance model below.[23]) About 10% of patients with an infectious gastroenteritis experience remaining IBS-like symptoms after the infection has healed. [24] This development may involve increased visceral sensitivity,[24] but also respondent conditioning,[25] and changes in the gut microbiota,[26] described below.

2.3.2   Gastrointestinal-specific anxiety and avoidance behaviors

Gastrointestinal-specific anxiety (GSA) is anxiety directed towards gastrointestinal symptoms.[27] GSA includes visceral sensitivity, vigilance toward symptoms, fear and worry about symptoms, and avoidant behavior.[27] In a study of 1021 university students where different aspects of anxiety were assessed GSA was found to be the strongest predictor of IBS.[28] Pathological GSA has been shown to occur in the absence of anxiety disorders and external stressors, and may therefore have a unique explanatory value of IBS.[28] GSA predicts gastrointestinal symptoms and quality of life in adults diagnosed with IBS.[29] Decreased GSA has been shown to mediate symptom change in psychological treatments for adults with IBS[30] but this has not been investigated in pediatric FAPDs. Avoidance behaviors are part of

the GSA construct but reduced avoidance behaviors have also independently been shown to mediate symptom improvement in adults[30,31] and adolescents[32] with IBS. The function of avoidance behaviors is usually to reduce unpleasant feelings or fears. Patients with FAPDs may avoid symptom-provoking foods and situations perceived as difficult to endure with symptoms. Avoidances may also include controlling strategies such as long toilet visits, distraction from symptoms, and safety behaviors like arranging to be picked up if symptoms should occur.

2.3.3 Pain perception and regulation

Abdominal pain or discomfort is the common feature for IBS, FD, and FAP-NOS. Pain is a naturally aversive stimuli and the inherent response for individuals who experience pain is to do something to reduce the pain. These reactions to pain, such as withdrawal from a dangerous situation or taking care of a wound, have evolutionary advantages because it protects the individual from further harm.

The International Association for the Study of Pain has the following definition of pain: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[33] Pain is a subjective experience that can be affected by factors like cognitions, interactions with others, and emotions. High or low pain can be classically conditioned to a neutral stimuli, which later affects perception of pain level when paired with moderate pain.[34] Attention to pain (vigilance), depressive mood, and anxiety towards pain are factors that have been shown to amplify pain perception.[35,36] Pain may both proceed and be proceeded by emotional distress in serial interactions.[37]

Nociceptive pain is pain that occurs as a consequence of tissue damage or an inflammatory process. Signals from nociceptors (pain receptors) are transported via nerves to the dorsal horn in the spinal cord where signals are reconnected to the brain. Pain signals may be amplified or inhibited both in the dorsal horn (bottom-up) and the brain (top-down).[35] In functional pain the brain receives pain signals without nociceptive stimulation or with only a low degree of nociceptive stimulation.[35] The human brain does not perceive nociceptive or functional pain differently. The visceral sensitivity seen in patients with FAPDs may be related to dysfunctions in pain modulatory systems. A study found that adolescents with FAPDs had impairments in conditioned pain modulation, compared with healthy controls. Conditioned pain modulation is thought to reflect reduced efficiency in descending inhibitory pain systems.[38] Such deficit in pain inhibition has also been shown in experimental studies in adults with IBS.[39,40]

2.3.4 Brain-gut axis and the gut microbiota

The quotation from Hippocrates "All disease begins in the gut" has gained increased validity in the last few years as the gut microbiota has been suggested to play a role not only in FAPDs,[41] but also in disorders like obesity, autism, and cardiovascular disease.[42] The gut microbiota consists of microorganisms within the gastrointestinal tract that are involved in a bidirectional communication between the gut and the brain, the brain-gut axis, involving the immune system, the hormonal system, and the neural system. Stress induced by maternal separation has been shown to change the microbiota in rhesus monkeys and mice[43,44] and

experimental change of the microbiota has been shown to affect behavior.[45] Cross-sectional studies have shown that some patients with IBS have a different gut microbiota compared with healthy controls while others do not seem to differ.[26] Most studies of the microbiota have been conducted within animal models, but it is a rapidly growing research field that may lead to future advancements in treatments for FAPDs and other conditions.[46] The hypothalamic pituitary axis, also known as the stress axis, is part of the brain-gut axis. The interactions within the brain-gut axis may help explain stress related associations such as the link between vulnerability to FAPDs in adulthood and traumatic experiences in childhood.[47] The role of stress is emphasized in many treatments for FAPDs and several protocols include relaxation techniques, as a way of coping with stressors.

2.3.5 Parents as context and the role of gender

There is a clustering of FAPDs within families, which is assumed to have both genetic and social learning explanations.[48-50] Parents are the most important persons for a child's development and constitute a major part of the child's context. Parents may both reinforce and model pain behaviors and fear toward pain stimuli. In a study by Walker et al,[51] parents were instructed to respond to their children's pain complaints by attention, distraction or with no specific instruction. Children who received attention for their pain complaints engaged twice as much in complaining compared with children in the no specific instruction-group. Children who were distracted complained half as much as children in the no specific instruction-group. The results for self-rated gastrointestinal symptoms were similar to the results for the pain complaints. Children rated distraction as more supportive than attention. The parents however, rated distraction as a possibly more harmful approach than attention. The study shows that parental behavior can influence a child's experience of gastrointestinal symptoms and that parents may contribute to both amplification and inhibition of their child's perceived pain. The same study also showed that attention from parents increased symptom complaints more for girls than for boys, which gives a potential lead as to why FAPDs are more prevalent in girls than in boys.[51] Expectations related to gender, where the sick-role might be more socially accepted in females, may contribute to the development and maintenance of FAPDs.

A review of experimental and observational studies concluded that parental responses to child pain behaviors seem to affect development and maintenance of functional abdominal pain [52]. Another study showed that family functioning was more related to pain-related disability than pain intensity in children with chronic pain [53]. This may be one explanation why some children are severely disabled by their abdominal pain whereas others are less hindered.

2.3.6 Anxiety, depression, and coping strategies

Anxiety and depression are associated with FAPDs but it is unclear whether they precede or are preceded by FAPDs. Like in pain perception and emotional distress this interaction may appear interchangeably.[37] However, a meta analysis of longitudinal studies showed that anxious and depressed mood provide a twofold risk of developing IBS in adults.[54]

Children with FAPDs have been shown to use more avoidant coping than children without abdominal pain.[55] In a cross-sectional study of children with FAPDs or inflammatory bowel disease (IBD) maladaptive coping styles such as catastrophizing and social isolation were

found to be associated with depression and functional disability for both groups. In the same study Van Tilburg et al also found that patients with FAPDs engaged in more coping, both positive and negative, than patients with IBD.[56] This might reflect that while medical treatments are available for children with IBD, children with FAPDs are more prone to rely on coping strategies. Another possible explanation is that the tendency to use coping mechanisms might contribute to the development of FAPDs. Catastrophizing about symptoms may lead to symptom prioritization and perception of symptoms as threatening, closely related to visceral sensitivity, vigilance and gastrointestinal-specific anxiety.

In a newly published article of recommendations for clinical practice, Keefer et al establishes that gastrointestinal disorders, both functional and those with a clear somatic cause, cannot be disentangled from their psychological context. The authors conclude that "the substantial burden of these diseases is co-determined by symptom and disease severity and the ability of patients to cope with their symptoms without significant interruption to daily life".[57] This conclusion generalizes far beyond gastrointestinal disorders, and will hopefully gain incdreased validity and influence in both somatic and psychiatric care.

2.4 THEORETICAL FRAMEWORKS

Interactions of factors related to FAPDs can be understood within different theoretical frameworks. The biopsychosocial model, the learning theory, and the fear and avoidance model are shortly described below. They are mutually inclusive and may all contribute to the understanding of the etiology of FAPDs.

2.4.1 The biopsychosocial model

The biopsychosocial model (BPS) was developed as a reaction to the biomedical perspective in which illness and disease are regarded as caused by purely biological mechanisms. The BPS was first described 1977 by Engel.[58] In the BPS biological, psychological, and social factors all play a role in development and course of illness and disease. The BPS has been particularly influential within the field of chronic pain.[59] Levy at al base their report of psychosocial aspects of FAPDs on the BPS and conclude that all aspects of the model need to be addressed in treatments for FAPDs,[60] which is also concluded in a recent overview of biopsychosocial aspects of FAPDs.[18] However, the BPS is general and does not give any guidance of how the different factors interact in the emergence of FAPDs and how they should be addressed in treatment.

2.4.2 Learning theory

According to the learning theory behaviors are learned via respondent conditioning, operant conditioning, or social learning. Respondent conditioning occur when a neutral stimulus is paired with a conditioned stimulus.[61] The stimuli must occur in close timing for learning to take place and repeated pairings are sometimes necessary. In an experimental study, participants responded with fear to a non-painful abdominal stimulus that had previously been paired with a painful abdominal stimulus.[25] Such learning may be present in the development of functional gastrointestinal disorders. Operant conditioning concerns learning via consequences, appearing after the behavior.[62] Reinforcement of a behavior increases the behavior's occurrence and punishment decreases it. Attention from parents can be a potent

reinforcer for different kinds of behaviors in children. Another powerful reinforcer is immediate symptom relief, which may occur as a consequence of avoidant behavior. Social learning or modeling is learning by imitation of behaviors.[63] Language, how to behave in social situations, and how to cope with stressors or pain may be learned via modeling. The strengths of learning theory include the firm ground of experimental studies of both animal and human behavior and its usability to understand how behaviors arise and how behaviors can be changed.

2.4.3 The fear and avoidance model

In the fear and avoidance model for chronic pain, pain can be interpreted as either fearful or harmless.[64] When pain is perceived as fearful, avoidance behavior is activated to protect the individual from harm. Avoidance behavior may also be activated by a perceived threat without the conscience feelings of fear.[65] A neutral stimulus, such as a non-painful abdominal signal, may be paired with an aversive stimulus, such as abdominal pain (respondent conditioning).[25,66] After this pairing the neutral stimulus too can provoke avoidance behavior. When pain is acute, avoidant behavior is an appropriate response, aiming to minimize damage to the individual. In functional pain however, avoidant behavior will operate together with fear of pain and vigilance to symptoms and maintain pain and disability.[23] In FAPDs, avoidant behaviors are often overt (such as avoidance of symptom-provoking food) but can also be covert (such as avoidance by distraction from symptoms). The avoidance prevents new learning of being able to cope with symptoms and a vicious circle of fear and avoidance is formed. The fear and avoidance model was originally developed for adults but is widely used in different settings and has shown a good fit for the development of functional disability in children and adolescents with chronic pain.[67]

2.5 TREATMENTS IN PEDIATRIC FAPDS

2.5.1 Non-psychological treatments
Cochrane reviews have found that the scientific support for the effectiveness of non-psychological treatments in pediatric FAPDs is weak. Pharmacological treatments are effective in adults[68], but for children they have not been able to show superiority compared with placebos.[69] A widely used elimination diet in IBS is the FODMAP diet, restricting foods with highly fermentable oligo-, di-, and monosaccharides, and polyols. It has been shown to decrease symptoms in adults with IBS,[70] but there is no support for the FODMAP diet in children.[71] Also, it can be argued that elimination diets restricting children's nutritional intake and pharmacological medications with potential side effects should not be first hand treatment choices for growing children. To eliminate gluten and lactose is common in both children and adults with FAPDs. However, in a recent double-blinded placebo-controlled randomized study adult participants with suspected non-coeliac gluten sensitivity did not experience more symptoms on days with gluten compared to on days with placebo.[72] Similarly, no difference in symptoms was found in a double-blinded placebo-controlled study where children with reported lactose sensitivity received lactose or placebo.[73] There is no support for fiber based interventions, but there is some support for the use of probiotics. However, recommendations on specific probiotics cannot yet be given.[71] Yoga therapy has not been proven effective in pediatric FAPDs.[74]

2.5.2 Psychological treatments

Cognitive behavioral therapy (CBT) and hypnotherapy have been shown to effectively reduce pain in pediatric FAPDs, but a recent Cochrane review concludes that the evidence is of low quality and includes only little proof of long-term benefits.[74] Also, evidence regarding improvements in quality of life, daily functioning, anxiety, and depression in CBT and hypnotherapy for pediatric FAPDs is lacking. However, two large randomized controlled trials not included in the Cochrane review[75,76] were recently published showing good results on several outcome measures, strengthening the support for CBT. There is no support for written self-disclosure in pediatric FAPDs.[74] Considering the high prevalence of FAPDs and the significant burden for children and their families there is a need for more high-quality research assessing not only symptoms, but also function and quality of life for children with FAPDs.[55]

2.5.3 Cognitive behavioral therapy (CBT)

CBT is an established form of treatment for both psychiatric and somatic conditions[77] and CBT is also the most studied psychological intervention in pediatric FAPDs.[74] However, many studies of CBT for pediatric FAPDs suffer from methodological limitations. Such limitations include small sample sizes, not pre-specified primary outcome measure, inadequately described interventions, and lack of relevant assessments such as function and quality of life. Large well-designed trials typically show smaller effect sizes than small trials of lower quality. For an overview of RCT:s of CBT for pediatric FAPDs from 1990 to this date, see Table 1.

The CBTs for FAPDs that have been tested in randomized controlled trials include a number of different components such as relaxation,[55,78-81] breathing exercises,[55,80,82] cognitive techniques for changing thoughts,[55,78,79,81] exposure exercises, [75] distraction techniques,[55,79,81,82] positive self-statements,[55,79,80,82] and parental interventions.[55,75,76,78-80,82] Most treatments consist of several components and it is not clear which ones are effective or what the potential working mechanisms are. Also, there is a risk that treatments use components that are not coherent and even pull in opposite directions.[32] Therefore there is a need for studies that can reveal active components and potential working mechanisms in CBT for FAPDs.[55,74]

Table 1. Randomized controlled trials of cognitive behavior therapy for pediatric FAPDs

Author (Year)	Inter-ventions	Sample Size (Mean age)	Assessed Symptoms	Assessed Function/diability	Assessed Quality of life	Strengths	Limitations
Lalouni (2018, not published)	10 weeks Internet-CBT vs. TAU	90 (10.2)	✓*	✓*	✓*	Includes health economy	TAU not standardized
Levy (2017)	Brief CBT vs. education and support	316 (9.4)	✓	✓*	✓*	Large sample Active control	No effect on primary outcome
Bonnert (2017)	10 weeks Internet-CBT vs. WL	101 (15.5)	✓*	✓*	✓*	Effects on a large range of measures	WL control
Groß and Warsch-burger (2013)	6 sessions in group vs. WL	29 (9.6)	✓*	-	✓*	Large effects	WL control Small study
Van der Veek (2013)	6 sessions vs. 6 sessions with pediatrician	104 (11.9)	✓	✓	✓	Potent control condition	No difference between groups
Levy (2010, 2013)	3 sessions family intervention vs. Education	200 (11.2)	✓ *	✓	-	Large sample Active control	Small effect sizes
Duarte (2006)	4 sessions family intervention vs. SC	32 (9.2)	✓ *	-	-	Effects in pain freq.	Small study
Robins (2005)	5 sessions family intervention vs. SC	86 (11.3)	✓ *	✓ *	-	Assessed school absence	Only completers analyses (n=69)
Sanders 1994	6 sessions family intervention vs. SC	44 (9.2)	✓ *	✓ *	-	Assessed treatment expectan-cies	No flow-chart or description of drop-outs

Vs. = Versus, TAU = Treatment as usual, SC = Standard care, WL = Waiting list, Freq. = frequency
✓= Assessed
* = Significant difference between groups

2.5.4 Exposure-based CBT

Exposure is a key component in CBT and improvements in child functioning after CBT for anxiety disorders have been related to the use of exposure exercises.[83] Exposures within CBT comprise exercises in which the patient provokes symptoms (interoceptive exposure), approach feared situations (in-vivo exposure), or imagine painful or intrusive thoughts, feelings, or memories (imaginal exposure). During the exposures the patient gains new experience of being able to cope with the symptoms, which is likely crucial for the improvement of symptoms and function. Exposure to painful stimuli may be particularly challenging to children and parents since symptom reduction usually do not occur as fast as in exposure for anxiety symptoms. Exposure exercises for patients with FAPDs include provoking symptoms by for example eating symptom-provoking food or wearing a tight belt (interoceptive exposure) and approaching difficult situations such as school or physical exercise (in-vivo exposure). It also includes minimizing control behaviors such as frequent toilet visits or extensive resting.

Exposure therapy was invented by Mary Cover Jones in the 1920's.[84] Jones conducted a series of experiments with young children and concluded that in-vivo exposure was the most effective method in reducing fear. Jones also concluded that social learning was helpful, but that discussion and distraction were ineffective. Exposure therapy is based on the principles of learning theory.

Craske et al developed a CBT protocol targeting gastrointestinal specific anxiety in adults with IBS that included interoceptive exposures to visceral sensations.[85] Craske et al concluded that the visceral sensitivity and vigilance in IBS resembled the sensitivity of bodily signals seen in panic disorder and modeled the treatment after exposure-based CBT for panic disorder.[86] The treatment was compared to stress management and attention control with results favoring CBT with interoceptive exposures. Ljótsson et al developed an exposure-based CBT protocol with both interoceptive and in-vivo exposures for adults with IBS. In Ljótsson's treatment the exposure exercises are accompanied by brief mindfulness exercises to increase the effects of the exposures. Several studies evaluating Ljótssons's treatment protocol delivered via the internet have shown large effects on both symptoms and quality of life.[87-90] The treatment has been proven to be superior to an intervention consisting of stress-reduction, relaxation, and dietary advice.[91] Exposure-based CBT has also been shown to be effective on a wide range of outcomes including symptom severity, quality of life, and daily functioning for adolescents with IBS.[75]

2.5.5 Engaging parents in the treatment

Engaging parents in the treatment for children do not necessarily increase the treatment effects. In fact, in a meta analysis of CBT for children with anxiety disorders treatments with or without parental involvement showed no significant differences in effect.[92] However, the comparison was hampered by the heterogeneity of components used in the parental modules. If the parental modules are of good quality and coherent with the overall treatment approach, the parents can act as co-therapists during treatment. Parents can also help their child sustain the treatment gains after the treatment has ended. In exposure-based CBT for FAPDs, parents can facilitate and encourage the child's exposure exercises, reinforce and model healthy

behaviors, and decrease attention to pain behaviors. Such parental strategies are highly compatible with the exposure-based approach. Indeed, not addressing parental behaviors may even undermine the treatment as some parents to children with pain disorders have a tendency to restrict their children's pain-inducing activities.[93] Parental involvement has been used in CBT-studies of FAPDs in combination with strategies for the child,[55,75,76,78-80,82,94] but to the best of our knowledge never in combination with exposure-based CBT for children 8-12 years.

2.5.6 Internet-delivered CBT

There is a shortage of CBT therapists in healthcare, which is why innovative ways of making CBT available for children with FAPDs are needed. A possible way of making CBT more available is to use internet-delivered CBT (Internet-CBT). In Internet-CBT the treatment content is delivered via texts, images, and film clips and therapist support is provided via text messages. Internet-CBT carries several advantages compared to CBT delivered in a traditional format with weekly visits at a clinic: patients can work with the treatment at any time during the week without taking time off from school or work, the treatment can be delivered regardless of the geographical distances, less therapist time per patient is needed, and the risk for therapist drift is small.[95]

Internet access is generally high among children. According to the Swedish Media Council 99% of all Swedish 9-12 year old children have internet access in their homes.[96] The number of trials of pediatric Internet-CBT do not match children's high access to the internet. We conducted a comprehensive review and meta-analysis of Internet-CBT for children and adolescents in 2016 and found only 19 studies from the fields of behavior medicine (n=10) and psychiatry (n=9) in our worldwide search.[95] Of the interventions within behavioral medicine eight out of 10 concerned pain conditions.[97-104] There is a gap between available treatments and the need of treatments for children with FAPDs. This thesis may help bridging that treatment gap by studying a treatment and delivery method that may be implemented on a broad scale, if proven effective.

2.5.7 Cost effectiveness

Given some of the advantages of Internet-CBT (e.g. less therapist time per patient and no time off from school or work) this form of treatment is potentially cost effective. In an evaluation of a brief telephone delivered CBT Levy et al concluded that the CBT intervention was more effective in reducing health care visits for abdominal pain and missed school days than an educational support, but a cost effectiveness analysis was not conducted.[76] Law et al conducted a cost effectiveness analyses of a randomized controlled trial for chronic pain[101] and concluded that Internet-delivered CBT was equally cost effective as an internet education intervention.[105] Exposure-based CBT delivered via the internet has been shown to be cost effective for adult IBS.[89,106] Internet-CBT has also been shown to be cost effective in pediatric obsessive compulsive disorder[107] but analyses of cost effectiveness in pediatric FAPDs are lacking.

2.6 SUMMARY OF THE BACKGROUND OF THE THESIS

Pediatric FAPDs are prevalent and associated with low quality of life, functional disability, and a high health care consumption. The etiology of FAPDs is multifactorial and includes biological, psychological, and social factors, which are all included in the biopsychosocial model. Etiological factors include visceral sensitivity and anxiety, vigilance to symptoms, altered pain regulation, and parental responses to the child's symptoms. Theoretical frameworks in which pediatric FAPDs can be understood are the learning theory and the fear and avoidance model. These theories give guidance about how psychological treatments can be designed and how parents and other important adults can respond to children with FAPDs.

Pharmacological and dietary treatments have not been proven effective for pediatric FAPDs, but the results for CBT are promising. Most CBT protocols studied in clinical trials include multiple components, which is why there is a need for studies that can reveal active components and potential working mechanisms in CBT for pediatric FAPDs.

3 AIMS

3.1 OVERALL AIM

The overall aim of the thesis was to develop and evaluate a psychological treatment for children with FAPDs that could help the children decrease their symptoms and increase their quality of life. Theoretically, the premise was to explore if and how exposure to abdominal symptoms and avoided situations were beneficial for young children with FAPDs. A further basis for the treatment was that it should be scalable. Therefore, the internet format was a chosen.

3.1.1 Study I

The aim of Study I was to develop an exposure-based CBT for children with FAPDs and to test its feasibility, acceptability, and potential effectiveness.

3.1.2 Study II

In Study II the treatment content from Study I was transformed into an internet treatment, Internet-CBT, and feasibility, acceptability, and potential effectiveness were again evaluated. We hypothesized that the treatment would be feasible, acceptable and potentially effective based on the results in Study I.

3.1.3 Study III

The aims of Study III were to assess effectiveness and cost effectiveness of the Internet-CBT compared with treatment as usual. We hypothesized that the Internet-CBT would be effective and cost effective.

3.1.4 Study IV

In Study IV we used data from Study III and the aim was to assess if gastrointestinal-specific anxiety and avoidance behaviors mediated a change in gastrointestinal symptoms for children receiving Internet-CBT compared with children receiving treatment as usual. A further aim was to assess if baseline values of the proposed mediators moderated the mediation.

4 EMPIRICAL STUDIES

4.1 THE INTERVENTION

The intervention was based on the exposure-based CBT for adults[90] and adolescents[75] with IBS and on parental support commonly used in parenting programs.[108,109] The main components in the treatment were exposure to symptoms and to situations in which symptoms were perceived as difficult to have or even intolerable. Since exposure to painful stimuli can be challenging for both children and their parents, emphasis was put on explaining the treatment rationale. The role of avoidant and controlling behaviors in maintaining and amplifying symptoms was stressed. In the parental modules, the role of parental reinforcement, such as attention to the child's pain behavior, was highlighted as a potential maintaining factor of the symptoms. Exposure to symptoms was presented as a means to decrease symptoms and limitations in the child's everyday life. The exposure exercises were based on challenging avoidances of symptom-provoking stimuli, avoided situations, control strategies, and safety behaviors, mapped by the child in the first module. A short mindfulness exercise: Stop, Observe, and Let go (SOL) was used by the children to increase the effect of the exposures. In SOL the children would first stop what they were doing, observe their abdominal symptoms for a short while, and then let go of their symptoms and continue to do what they were doing before. The therapist encouraged the child to increase the difficulty of the exposure exercises during the treatment. Most parents used a printed token game to reinforce their child's work with exposure exercises, while others preferred to encourage their child's work in another way. In Study I the intervention was developed and evaluated face-to-face at the clinic. After Study I the treatment was adapted to the internet format (Internet-CBT) and used in the Studies II-IV.

4.2   THE INTERVENTION VIA INTERNET

The Internet-CBT was delivered via the BIP platform, using child-adapted templates supporting texts, images, sound files, and video material. The BIP platform has previously been used in randomized controlled trials of pediatric anxiety disorders,[110] obsessive-compulsive disorder,[111] and irritable bowel syndrome.[75] The Internet-CBT consisted of 10 modules for the children and 10 modules for the parents. Parents and children worked with the child modules together. Both parents, if applicable, were encouraged to take part of the parental modules. Therapist support consisted of written comments and messages within the treatment platform. Additional telephone calls were used if further support was needed.
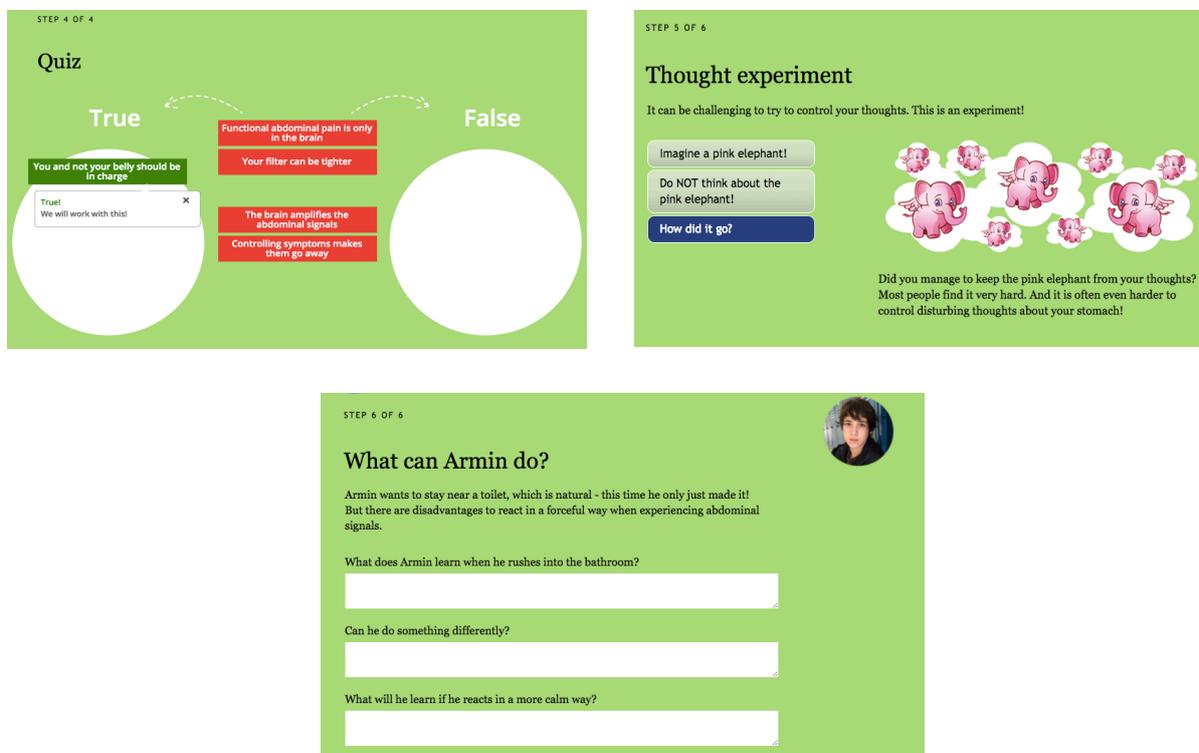
Figure 1. Screenshots from Internet-CBT

4.3 STUDY I: EXPOSURE-BASED COGNITIVE BEHAVIOR THERAPY FOR CHILDREN WITH ABDOMINAL PAIN: A PILOT TRIAL

Aim

The aim of Study I was to develop and evaluate the treatment protocol of exposure-based cognitive behavioral therapy for children with abdominal pain and their parents. The evaluation included potential efficacy, feasibility, and acceptability.

Methods

We included 20 children 8-12 years with pain-related functional gastrointestinal disorders (Rome III criteria) and their parents in this open study. The participants came to the clinic once a week for 10 weeks and received face-to-face cognitive behavioral therapy based on exposure exercises and parental support. Attendance to the sessions, engagement in the exposure exercises, satisfaction with treatment, and perceived usefulness were measures of feasibility and acceptability. Within-group effects from baseline to post-treatment and from baseline to 6-month follow-up were calculated using two-tailed dependent t-tests. The primary outcome was pain intensity and secondary measures included gastrointestinal symptoms, quality of life, anxiety, school absenteeism, and parental responses to the child's pain behavior.

Main Results

Satisfaction with the treatment and attendance to the sessions were high. Children engaged in the exposure exercises to a large extent and perceived the treatment to be useful. The children showed significant improvements in pain intensity from baseline to post-treatment with a small effect size (Cohen's d=0.40, P=0.049). The results were further improved at 6-month follow-up showing a large effect size (d=0.85, P=0.004). Significant improvements were also seen at post-treatment in gastrointestinal symptoms, quality of life, anxiety, school absenteeism, and parental responses to the child's pain behavior. These results were maintained or further improved at 6-month follow-up.

4.4 STUDY II: INTERNET-DELIVERED COGNITIVE BEHAVIORAL THERAPY FOR CHILDREN WITH PAIN-RELATED FUNCTIONAL GASTROINTESTINAL DISORDERS: FEASIBILITY STUDY

Aim

In Study II the aim was to evaluate the treatment developed in Study I, which was now adapted to the internet (Internet-CBT), for children with abdominal pain and their parents. The evaluation included potential efficacy, feasibility, and acceptability.

Methods

We included 31 children 8-12 years with pain-related functional gastrointestinal disorders (Rome III criteria) and one of their parents in the study. We used a within-group design with measures conducted at baseline, post-treatment, and at 6-month follow-up. Primary outcome was child-rated gastrointestinal symptoms. Secondary outcomes included quality of life, pain intensity, gastrointestinal-specific anxiety, school absence, and parental responses to the child's pain behavior. Feasibility and acceptability were assessed with measures of treatment satisfaction, subjective treatment effect, and number of completed modules. Multi-level linear mixed models were used to estimate means and Cohen's d effect sizes. The treatment was therapist guided Internet-CBT with 10 weekly modules for both children and their parents.

Main Results

At the post-assessments the within-group effect size was large and significant for the primary outcome child-rated gastrointestinal symptoms (d=1.14, P<0.001), which was maintained at 6-month follow-up (d=1.40, P<0.001). Results for quality of life, pain intensity, gastrointestinal-specific anxiety, school absence, and parental responses to the child's pain behavior were also significant and within group effect sizes varied between medium and large for both parents' and children's assessments. From baseline to 6-month follow-up all these measures showed a large within group effect size. Both children and parents expressed overall satisfaction with the treatment and most participants reported a positive treatment effect. Attendance to the treatment was high among both children and parents.

4.5 STUDY III: EFFECTIVENESS AND COST EFFECTIVENESS OF COGNITIVE BEHAVIOURAL THERAPY VIA INTERNET FOR CHILDREN WITH FUNCTIONAL ABDOMINAL PAIN DISORDERS: A RANDOMIZED CONTROLLED TRIAL

Aim

The aim in Study III was to compare the effectiveness and cost effectiveness of Internet-CBT and treatment as usual for children with functional abdominal pain disorders and their parents.

Methods

We included 90 children 8-12 years with functional abdominal pain disorders (Rome IV criteria) and one of their parents. Participants were randomized to 10 weeks Internet-CBT with therapist support or treatment as usual. Assessments were conducted at baseline, weekly during treatment, at 10-week follow-up (post-assessment) and at 6-month follow-up. Primary outcome was child-rated gastrointestinal symptoms and secondary outcome measures included quality of life, gastrointestinal-specific anxiety, avoidance behaviors, and parental responses to the child's pain behavior. Significant interaction effects between group and time based on restricted maximum likelihood mixed models were interpreted as effects of treatment. Effect sizes between and within groups were calculated as Cohen's *d*. Costs for health care consumption and loss of productivity were collected at baseline, week 6 during the treatment and at 10-week follow-up. Generalized linear models were used to assess changes in mean cumulative costs between groups, controlling for baseline values.

Main Results

Children receiving Internet-CBT improved significantly with a medium effect size on the primary outcome gastrointestinal symptoms compared with treatment as usual (*d*=0.46, P=0.022). Improvements in the secondary outcomes quality of life, gastrointestinal-specific anxiety, avoidance behaviors, and parental responses to the child's pain behavior were also in favor of Internet-CBT. Internet-CBT was found to be highly cost effective compared with treatment as usual. From the societal perspective there was a cost saving of US$1050 for every child who received Internet-CBT instead of treatment as usual. Children receiving Internet-CBT used significantly less health care resources during treatment compared with children receiving treatment as usual.

4.6 STUDY IV: MEDIATION AND MODERATION OF FEAR AND AVOIDANCE IN COGNITIVE BEHAVIOURAL THERAPY FOR CHILDREN WITH FUNCTIONAL ABDOMINAL PAIN DISORDERS.

Aim

In Study IV, data from the randomized controlled trial in Study III were used. The aim was to assess if gastrointestinal-specific anxiety and avoidance behaviors mediated a change in gastrointestinal symptoms for children receiving Internet-CBT compared with children receiving treatment as usual, and if baseline values of the proposed mediators moderated the mediation.

Methods

We used bi-weekly assessments of the proposed mediators gastrointestinal-specific anxiety and avoidance behaviors from the 90 included children (ages 8-12 years) with FAPDs and weekly assessments of children's gastrointestinal symptoms assessed by the children's parents. Univariate and multivariate growth models were used to test direct effects of the treatment on the outcome and the indirect effects of the proposed mediators and the moderated mediation.

Main Results

In the model, the treatment group significantly predicted the outcome, in favor of Internet-CBT, consistent with the results in Study III. Also, treatment condition significantly predicted the slope of the proposed mediators (*a*-path) in favor of Internet-CBT and the proposed mediators were correlated with the outcome (*b*-path). The indirect effects of the cross-product of these paths (*ab*) were significantly different from zero for both gastrointestinal-specific anxiety $ab = 1.58$, 95% CI (0.43, 3.33) and avoidance behaviors $ab = 1.43$, 95% CI (0.42, 3.23). Further, baseline levels of the mediators moderated the mediation.

4.7   ETHICAL CONSIDERATIONS

In all research, and particularly in research with children as participants, a thorough consideration of the ethical aspects of the procedures and methods is necessary. All studies included in the thesis were reviewed and approved by the Regional Ethical Review Board in Stockholm. Ethical aspects of particular consideration in the included studies were 1) the safety of the recruitment procedure, 2) the child's informed consent, and 3) the safety of the technology used for assessments and treatment. The ethical considerations concerning these aspects are described below.

To minimize the risk of including children in need of a medical treatment, all children were assessed by their physician before inclusion. The physicians certified that proper medical examinations had been performed to support the FAPD diagnosis. The studies' PI, who is a pediatric gastroenterologist, had before Study I in consensus with other pediatric gastroenterologists decided which tests were obligatory.

A clinical psychologist interviewed all children and their parents before inclusion in the study. During this interview, psychiatric comorbidity was assessed with the Mini International Neuropsychiatric Interview.[112] In one part of the interview, the child was alone with the psychologist. During this time the child was asked about school, friends, family, and if somebody had done anything against his or her will, such as hitting or touching in a way he or she did not want to be touched. This procedure was used to screen for psychosocial problems and abuse, which has been reported to be overrepresented in patients with FAPDs.[60] If psychiatric illness, abuse, or psychosocial problems in need of immediate or other care were found, children were referred to appropriate treatments. All children included in the studies were enrolled as patients at the research clinic, which facilitated treatment documentation and referrals within the healthcare system. A child psychiatrist and the PI pediatric gastroenterologist were available for consultations during both the inclusion process and the treatment.

Before the children and parents came to the clinic, they received written information about the research project and during the clinical interview; the psychologist gave a description of the study. The children were then asked if they wanted to join the study and were informed that they could cancel participation at any time, even if their parent(s) wanted to continue. If they wanted to participate in the study, the child gave oral consent and the parents gave written consent.

The login to the treatment and the online assessments were accessed via a two-factor authentication, where the personalized logins and passwords were confirmed via text messages to the participants' mobile phones, in accordance with regulations by the Swedish National Board of Health and Welfare. There is an ongoing discussion about technological security within BUP KFE (Child and Adolescent Psychiatry Clinical Research Unit) involving the BIP-team and the developers. The security of the online platform is of major importance and as technology advances the development of safety measures will continue.

5 DISCUSSION

5.1 IS EXPOSURE-BASED CBT, FACE-TO-FACE OR ONLINE, FEASIBLE AND ACCEPTABLE FOR CHILDREN WITH FAPDS?

Exposure to painful stimuli was a key component in the treatments and this was hypothesized to be difficult for both children and their parents. In exposure for pain, the symptom relief is usually delayed compared with the symptom relief seen in exposures for anxiety symptoms, which is why pain-provoking exposures can be very challenging. Also, the intervention included strategies to decrease parental reinforcement of their child's pain behaviors, which was thought to be a tough eye-opener for some of the parents, who may have been reinforcing these behaviors for several years. In the face-to-face study (Study I) the therapist helped the families during the weekly sessions to adjust the level of difficulty of the exposure exercises so that it was acceptable but challenging throughout the treatment. All children in the study engaged in exposure exercises and most parents welcomed the parental strategies. The children and their parents attended a mean of 9.3/10 (93%) sessions and all children declared that the treatment had been helpful in dealing with their symptoms. Almost all children 19/20 (95%) were satisfied with the treatment.

Before Study II, the treatment protocol used in Study I was converted into texts, images and animated films in 10 internet modules for children and parents, respectively. The main concerns were if children would engage in exposures without the face-to-face contact with the therapist and if this would increase the burden for the parents. Qualitative interviews with the parents (not reported in the thesis) showed that some parents were burdened by the intervention. However, 25/31 (81%) of the children completed 9 or 10 of the 10 treatment modules and 28/30 (90%) declared that the treatment had been helpful in dealing with their symptoms. There were no data available on the use of exposure exercises, but there were large within-group effect sizes of gastrointestinal symptoms (d=1.14, 95% CI 0.69-1.61), avoidance behavior (d=1.18, 95% CI 0.76-1.65), and gastrointestinal-specific anxiety (d=0.92, 95% CI 0.56-1.31), which suggests a successful use of the exposure-based treatment. In summary the exposure-based CBT seems to be feasible and acceptable to children and parents, both in a face-to-face setting and when delivered online.

5.2 IS INTERNET-CBT CLINICALLY EFFECTIVE FOR CHILDREN WITH FAPDS?

In Study III the treatment as usual group had higher symptom levels on the primary outcome measure at baseline compared with the Internet-CBT group, which may have been beneficial for the treatment as usual group. A more pronounced effect for participants with high levels of symptoms at baseline has been observed in pediatric pain patients.[113] However, the participants in Internet-CBT showed significantly greater reductions on both the primary outcome and on most secondary outcomes including quality of life and avoidance behavior (also measuring daily functioning). The differences in effect sizes were moderate to large and the gains were maintained at 6-month follow-up for children in Internet-CBT. Therefore, the

firm conclusion is that Internet-CBT based on exposure exercises for children with FAPDs is clinically effective.

5.3   IS INTERNET-CBT COST EFFECTIVE FOR CHILDREN WITH FAPDS?

We hypothesized that Internet-CBT would be cost effective; both because adult studies of Internet-CBT in IBS had shown cost effectiveness[89,106] and because we assumed that the expected effects gained would weigh more heavily than the additional costs of the low-resource intervention. The results exceeded our expectations. Not only was Internet-CBT cost effective, but also cost saving. For every child treated with Internet-CBT instead of treatment as usual a gain of US$1050 was obtained. The statistical method used (generalized linear models) controlled for baseline differences. There was a 92% probability that Internet-CBT was cost effective compared with treatment as usual.

The result in a cost effectiveness analysis is explained by two factors: differences in costs and differences in gains. The children in treatment as usual consumed significantly more healthcare resources than the children in Internet-CBT. They were also more impaired by reduced efficiency in school and school absence during treatment, even if this difference was not statistically significant. Gains in quality adjusted life years (QALYs) were observed for Internet-CBT, but not for treatment as usual, resulting in a statistically significant difference in QALYs in favor of Internet-CBT.

5.4   DO GASTROINTESTINAL-SPECIFIC ANXIETY AND AVOIDANCE BEHAVIOR MEDIATE CHANGE IN GASTROINTESTINAL SYMPTOMS?

Treatments should ideally be based on knowledge of its cause and operating mechanisms.[114] To shed some light on this we conducted the mediation analyses. We found that there was a significant treatment effect on the outcome in favor of Internet-CBT, similar in magnitude to the one found in Study III. We also found that treatment predicted the slope of the proposed mediators and that the mediators were correlated with the outcome. We conducted analyses of moderated mediation, using the baseline values of the mediators as moderators. The moderated mediation was significant for both gastrointestinal-specific anxiety and avoidance behavior indicating that children with higher baseline values on the mediators had a larger mediated effect. These analyses add further support to the role of gastrointestinal-specific anxiety and avoidance behavior as mediators of change and indicate that exposure-based CBT may be particularly valuable for children with high levels of symptom-specific fear and avoidance.

5.5   LIMITATIONS

There are some important limitations to the studies in this thesis. In Study I-II there were no control groups, which precludes causal inferences of the treatment effects. In all studies the children's parents had a higher mean educational level than the mean educational level in Sweden, which decreases the generalizability of the results. In the first two studies 64% and in the RCT 77% of the parents had a university degree, compared with 56% of the females,

and 49% of both males and females in Sweden in the same age group (in the RCT 86% of the parents were female). There was a nationwide recruitment in Study II and III but the participants had to pay from their own pocket for one obligatory trip to Stockholm (or persuade their county council to pay the tickets). This procedure has likely resulted in a selected group with parents being very motivated, particularly the ones that had traveled very far (range 0.3-854 km). On the other hand, physicians within primary, secondary, and tertiary healthcare referred all participants to the study, which increases the generalizability of the study.

5.6 CLINICAL IMPLICATIONS

Considering the fine results of Internet-CBT for children (seen in the studies I-III) and adolescents with FAPDs,[75] the high prevalence of pediatric FAPDs,[6] and the low quality of life seen in the patient group,[14] Internet-CBT should be made available to children and adolescents with FAPDs. Many families with children or adolescents with FAPDs seek healthcare,[15] but since there are no evidence-based treatment options available for them the benefits are often small while the costs are high.

Internet-CBT could either be situated within local units, such as primary or secondary healthcare centers, or it could be administered from a national internet unit like www.internetpsykiatrienheten.se for adults serving patients from all over Sweden. After a few days education CBT-psychologists could become therapists in Internet-CBT, based on knowledge obtained in an ongoing implementation study conducted within the research group.

In our Internet-CBT studies we only met the children and parents once, which was before the inclusion to the study. This procedure made it possible to include children living in remote areas in Sweden. However, if the treatment is implemented in a regional setting it may be wise to follow up the intervention with a regular face-to-face meeting after treatment completion. If the treatment is implemented in a national setting, the patients' local physician can follow up the patients face-to-face after the treatment.

5.7 FUTURE DIRECTIONS

In Study IV we found that children with high levels on avoidance and gastrointestinal-specific anxiety at baseline showed a more pronounced mediating effect than children with low levels of the mediators at baseline. The treatment contains several examples of children with explicit avoidance behaviors and fear of symptoms (e.g., avoiding onion or being afraid of physical training) but no examples of more subtle avoidances (e.g., keeping a full schedule to distract from symptoms). For children with subtle avoidances the therapist emphasized the work with the mindfulness exercise to increase exposure of symptoms and decrease distraction. Likely there is room for improvement in the treatment by including examples of different kinds of avoidances and providing guidance on how to work with these.

An interesting research question for the future is to assess whether there are different working mechanisms at play in treatments with theoretically different approaches for pediatric FAPDs and also if it is possible to identify which children would benefit most from the respective treatments. Hypnotherapy is alongside with CBT the treatment with the strongest empirical support in pediatric FAPDs. As many CBT protocols include relaxation, which has similarities to hypnotherapy, it would be interesting to compare hypnotherapy to exposure-based CBT, where relaxation is not included.

Another research approach is to dig deeper into which factors contribute to emergence, maintenance, and relief of symptoms in experimental models. It is challenging to isolate any factors and particularly factors that may overlap or co-occur, such as symptom-related fear and avoidance. However, such efforts may be rewarding as information on working mechanisms can inform both the work with improving treatments and the development of preventative methods.

6 CONCLUSIONS

Internet-CBT can be recommended for children 8-12 years with FAPDs, and particularly to children with high levels of gastrointestinal-specific anxiety or children who are limited by their symptoms. The treatment has the potential to increase treatment availability and decrease suffering for a large group of children. Internet-CBT can reduce costs, both to families, to the healthcare system, and for society compared with regular care.

7 ACKNOWLEDGEMENTS

Mamma and **pappa**, thank you for your continuous support! And thank you for being so nonneurotic, uncontrolling, and loving to Dante, Estrid, Jalal, and me! **Pelle**, my best brother and **Viktoria**, **Linnéa**, **Julia**, **Billy** and **Klara**, I´m so happy to have you in my life and could only wish you lived a little bit closer☺!

Dante and **Estrid**, thank you for teaching me how to be a better person and parent! I love you forever and always! I promise you will see me without the computer attached to my fingers in the near future!

Dear **Jalal**! Thank you for being my dearest friend and loving partner! I´d be lost without you!

8 REFERENCES

1.   Apley J, Naish N. Recurrent Abdominal Pains: A Field Survey of 1,000 School Children. Arch Dis Child. BMJ Publishing Group Ltd and Royal College of Paediatrics and Child Health; 1958 Apr 1;33(168):165–70.

2.   Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology. 2006 Apr;130(5):1527–37.

3.   Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology. 2016 Feb 15;150(6):1456–68.

4.   Edwards T, Friesen C, Schurman JV. Classification of pediatric functional gastrointestinal disorders related to abdominal pain using Rome III vs. Rome IV criterions. BMC Gastroenterology 2011 11:1. 2018;18(1):41.

5.   Robin SG, Keller C, Zwiener R, Hyman PE, Nurko S, Saps M, et al. Prevalence of Pediatric Functional Gastrointestinal Disorders Utilizing the Rome IV Criteria. J Pediatr. 2018 Apr;195:134–9.

6.   Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. Zhang L, editor. PLoS ONE. 2015;10(5):e0126982.

7.   Olén O, Neuman Å, Koopmann B, Ludvigsson JF, Ballardini N, Westman M, et al. Allergy-related diseases and recurrent abdominal pain during childhood - a birth cohort study. Aliment Pharmacol Ther. 2014 Dec;40(11-12):1349–58.

8.   Uusijärvi A, Alm J, Lindblad F, Olén O. Irritable bowel syndrome and functional abdominal pain in five-year-old children are related to lifestyle. Acta Paediatrica. 2016 Aug;105(8):971–8.

9.   Saps M, Seshadri R, Sztainberg M, Schaffer G, Marshall BM, Di Lorenzo C. A prospective school-based study of abdominal pain and other common somatic complaints in children. J Pediatr. 2009 Mar;154(3):322–6.

10.   Campo JV, Di Lorenzo C, Chiappetta L, Bridge J. Adult outcomes of pediatric recurrent abdominal pain: do they just grow out of it? Pediatrics. 2001;108(1):e1–e1.

11.   Horst S, Shelby G, Anderson J, Acra S, Polk DB, Saville BR, et al. Predicting persistence of functional abdominal pain from childhood into young adulthood. Clin Gastroenterol Hepatol. 2014 Dec;12(12):2026–32.

12.   Cunningham NR, Jagpal A, Peugh J, Farrell MK, Cohen MB, Mezoff AG, et al. Risk Categorization Predicts Disability in Pain-associated Functional Gastrointestinal Disorders After 6 Months. J Pediatr Gastroenterol Nutr. 2017 May;64(5):685–90.

13.   Youssef NN, Murphy TG, Langseder AL, Rosh JR. Quality of life for children with functional abdominal pain: a comparison study of patients" and parents" perceptions. Pediatrics. 2006 Jan;117(1):54–9.

14.   Varni JW, Bendo CB, Nurko S, Shulman RJ, Self MM, Franciosi JP, et al. Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases. J Pediatr. 2015 Jan;166(1):85–90.

15.   Olén O, Uusjärvi A, Grimheden P, Grahnquist L. Regionalt vårdprogram: Smärtdominerade funktionella mag-tarmsjukdomar hos barn och ungdomar. 2013 Apr 15;:1–60.

16.   Dhroove G, Chogle A, Saps M. A million-dollar work-up for abdominal pain: is it worth it? J Pediatr Gastroenterol Nutr. 2010 Nov;51(5):579–83.

17.   Hoekman DR, Rutten JMTM, Vlieger AM, Benninga MA, Dijkgraaf MGW. Annual Costs of Care for Pediatric Irritable Bowel Syndrome, Functional Abdominal Pain, and Functional Abdominal Pain Syndrome. J Pediatr. 2015 Nov;167(5):1103–8.

18.   Van Oudenhove L, Drossman DA, Halpert AD, Lackner JM. Biopsychosocial Aspects of Functional Gastrointestinal Disorders. Gastroenterology. 2016 Feb 18;:1355–1367.e2.

19.   Zhou Q, Verne GN. New insights into visceral hypersensitivity--clinical implications in IBS. Nat Rev Gastroenterol Hepatol. 2011 Jun;8(6):349–55.

20.   Van Ginkel R, Voskuijl WP, Benninga MA, Taminiau JA, Boeckxstaens GE. Alterations in rectal sensitivity and motility in childhood irritable bowel syndrome. Gastroenterology. 2001 Jan;120(1):31–8.

21.   Simrén M, Tornblom H, Palsson OS, van Tilburg MAL, Van Oudenhove L, Tack J, et al. Visceral hypersensitivity is associated with GI symptom severity in functional GI disorders: consistent findings from five different patient cohorts. Gut. 2017 Jan 19;:gutjnl–2016–312361.

22.   Wolitzky-Taylor K, Craske MG, Labus JS, Mayer EA, Naliboff BD. Visceral sensitivity as a mediator of outcome in the treatment of irritable bowel syndrome. Behav Res Ther. 2012 Oct;50(10):647–50.

23.   Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000 Apr;85(3):317–32.

24.   Mayer EA, Tillisch K. The Brain-Gut Axis in Abdominal Pain Syndromes. Annual Review of Medicine. 2011;62(1):381–96.

25.   Ceunen E, Zaman J, Weltens N, Sarafanova E, Arijs V, Vlaeyen JWS, et al. Learned Fear of Gastrointestinal Sensations in Healthy Adults. Clin Gastroenterol Hepatol. 2016 Nov;14(11):1552–2.

26.   Labus JS, Hollister EB, Jacobs J, Kirbach K, Oezguen N, Gupta A, et al. Differences in gut microbial composition correlate with regional brain volumes in irritable bowel syndrome. Microbiome. 2017 May 1;5(1):49.

27. Labus JS, Bolus R, Chang L, Wiklund I, Naesdal J, Mayer EA, et al. The Visceral Sensitivity Index: development and validation of a gastrointestinal symptom-specific anxiety scale. Aliment Pharmacol Ther. 2004 Jul 1;20(1):89–97.

28. Hazlett-Stevens H, Craske MG, Mayer EA, Chang L, Naliboff BD. Prevalence of irritable bowel syndrome among university students. J Psychosom Res. 2003;55(6):501–5.

29. Clevers E, Tack J, Tornblom H, Ringstrom G, Luyckx K, Simrén M, et al. Development of Irritable Bowel Syndrome Features Over a 5-year Period. Clin Gastroenterol Hepatol. 2018 Mar 3.

30. Windgassen S, Moss-Morris R, Chilcot J, Sibelli A, Goldsmith K, Chalder T. The journey between brain and gut: A systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome. Br J Health Psychol. 2017 Jun 1;13(19):171.

31. Hesser H, Hedman-Lagerlof E, Andersson E, Lindfors P, Ljótsson B. How does exposure therapy work? A comparison between generic and gastrointestinal anxiety-specific mediators in a dismantling study of exposure therapy for irritable bowel syndrome. J Consult Clin Psychol. 2018 Mar;86(3):254–67.

32. Bonnert M, Olén O, Bjureberg J, Lalouni M, Hedman-Lagerlof E, Serlachius E, et al. The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: A mediation analysis. Behav Res Ther. 2018 Mar 28;105:27–35.

33. Merskey H, Bogduk N. Classification of Chronic Pain. International Assn for the Study of Pain; 1994. 1 p.

34. Jensen K, Kirsch I, Odmalm S, Kaptchuk TJ, Ingvar M. Classical conditioning of analgesic and hyperalgesic pain responses without conscious awareness. Proc Natl Acad Sci USA. 2015 Jun 23;112(25):7863–7.

35. Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. Neuron. 2007 Aug 2;55(3):377–91.

36. Wiech K, Tracey I. The influence of negative emotions on pain: behavioral effects and neural mechanisms. Neuroimage. 2009 Sep;47(3):987–94.

37. Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science. 2000 Jun 9;288(5472):1769–72.

38. Morris MC, Walker LS, Bruehl S, Stone AL, Mielock AS, Rao U. Impaired conditioned pain modulation in youth with functional abdominal pain. Pain. 2016 Oct;157(10):2375–81.

39. Piché M, Arsenault M, Poitras P, Rainville P, Bouin M. Widespread hypersensitivity is related to altered pain inhibition processes in irritable bowel syndrome. Pain. 2010 Jan;148(1):49–58.

40.   Wilder-Smith CH, Robert-Yap J. Abnormal endogenous pain modulation and somatic and visceral hypersensitivity in female patients with irritable bowel syndrome. ncbinlmnihgov. World J Gastroenrerol. Jul;13(27):3699-3704

41.   Moloney RD, Johnson AC, O'Mahony SM, Dinan TG, Greenwood-Van Meerveld B, Cryan JF. Stress and the Microbiota-Gut-Brain Axis in Visceral Pain: Relevance to Irritable Bowel Syndrome. Munro G, editor. CNS Neurosci Ther. 2016 Feb;22(2):102–17.

42.   Carding S, Verbeke K, Vipond DT, Corfe BM, Owen LJ. Dysbiosis of the gut microbiota in disease. Microb Ecol Health Dis. 2015;26:26191.

43.   Bailey MT, Coe CL. Maternal separation disrupts the integrity of the intestinal microflora in infant rhesus monkeys. Dev Psychobiol. 1999 Sep;35(2):146–55.

44.   O'Mahony SM, Marchesi JR, Scully P, Codling C, Ceolho A-M, Quigley EMM, et al. Early life stress alters behavior, immunity, and microbiota in rats: implications for irritable bowel syndrome and psychiatric illnesses. Biological Psychiatry. 2009 Feb 1;65(3):263–7.

45.   Thomas RH, Meeking MM, Mepham JR, Tichenoff L, Possmayer F, Liu S, et al. The enteric bacterial metabolite propionic acid alters brain and plasma phospholipid molecular species: further development of a rodent model of autism spectrum disorders. J Neuroinflammation. 2012 Jul 2;9(1):153.

46.   Moloney RD, O'Mahony SM, Dinan TG, Cryan JF. Stress-induced visceral pain: toward animal models of irritable-bowel syndrome and associated comorbidities. Front Psychiatry. 2015;6:15.

47.   Chitkara DK, van Tilburg MAL, Blois-Martin N, Whitehead WE. Early life risk factors that contribute to irritable bowel syndrome in adults: a systematic review. Am J Gastroenterol. 2008 Mar;103(3):765–74.

48.   Levy RL, Jones KR, Whitehead WE, Feld SI, Talley NJ, Corey LA. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. Gastroenterology. 2001 Oct;121(4):799–804.

49.   Saito YA. The role of genetics in IBS. Gastroenterol Clin North Am. 2011 Mar;40(1):45–67.

50.   Henström M, Zucchelli M, Söderhäll C, Bergström A, Kere J, Melén E, et al. NPSR1 polymorphisms influence recurrent abdominal pain in children: a population-based study. Neurogastroenterol Motil. 2014 Oct;26(10):1417–25.

51.   Walker LS, Williams SE, Smith CA, Garber J, Van Slyke DA, Lipani TA. Parent attention versus distraction: Impact on symptom complaints by children with and without chronic functional abdominal pain. Pain. 2006 May;122(1-2):43–52.

52.   Levy RL. Exploring the intergenerational transmission of illness behavior: from observations to experimental intervention. Annals of behavioral medicine: a publication of the Society of Behavioral Medicine. 2011 Apr;41(2):174–82.

53.   Lewandowski AS, Palermo TM, Stinson J, Handley S, Chambers CT. Systematic review of family functioning in families of children and adolescents with chronic pain. J Pain. 2010 Nov;11(11):1027–38.

54.   Sibelli A, Chalder T, Everitt H, Workman P, Windgassen S, Moss-Morris R. A systematic review with meta-analysis of the role of anxiety and depression in irritable bowel syndrome onset. Psychol Med. 2016 Sep 8;46(15):1–16.

55.   Van Der Veek SMC, Derkx BHF, Benninga MA, Boer F, De Haan E. Cognitive behavior therapy for pediatric functional abdominal pain: a randomized controlled trial. Pediatrics. 2013 Nov;132(5):e1163–72.

56.   van Tilburg MAL, Claar RL, Romano JM, Langer SL, Walker LS, Whitehead WE, et al. Role of Coping With Symptoms in Depression and Disability: Comparison Between Inflammatory Bowel Disease and Abdominal Pain. J Pediatr Gastroenterol Nutr. 2015 Oct;61(4):431–6.

57.   Keefer L, Palsson OS, Pandolfino JE. Best Practice Update: Incorporating Psycho-gastroenterology into Management of Digestive Disorders. Gastroenterology. 2018 Jan 31.

58.   Engel G. The need for a new medical model: a challenge for biomedicine. Science. 1977 Apr 8;196(4286):129–36.

59.   Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007 Jul;133(4):581–624.

60.   Levy RL, Olden KW, Naliboff BD, Bradley LA, Francisconi C, Drossman DA, et al. Psychosocial aspects of the functional gastrointestinal disorders. Gastroenterology. 2006 Apr;130(5):1447–58.

61.   Pavlov PI. Conditioned reflexes: An investigation of the physiological activity of the cerebral cortex. Ann Neurosci. 2010 Jul;17(3):136–41.

62.   Skinner BF. The Behavior of Organisms. B. F. Skinner Foundation; 1938. 1 p.

63.   Bandura A, Jones MR. Social Learning Through Imitation. 1962. 1 p.

64.   Lethem J, Slade PD, Troup JD, Bentley G. Outline of a Fear-Avoidance Model of exaggerated pain perception--I. Behav Res Ther. 1983;21(4):401–8.

65.   LeDoux J. Anxious. Vol. 53, Journal of Behavior Therapy and Experimental Psychiatry. Penguin; 2016.

66.   LeDoux JE, Moscarello J, Sears R, Campese V. The birth, death and resurrection of avoidance: a reconceptualization of a troubled paradigm. Mol Psychiatry. 2017 Jan;22(1):24–36.

67.   Simons LE, Kaczynski KJ. The Fear Avoidance model of chronic pain: examination for pediatric application. J Pain. 2012 Sep;13(9):827–35.

68. Ford AC, Quigley EMM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. Effect of antidepressants and psychological therapies, including hypnotherapy, in irritable bowel syndrome: systematic review and meta-analysis. Am J Gastroenterol. 2014 Sep;109(9):1350–65.

69. Martin AE, Newlove Delgado TV, Abbott RA, Bethel A, Thompson Coon J, Whear R, et al. Pharmacological interventions for recurrent abdominal pain in childhood. Martin AE, editor. Cochrane database of systematic reviews (Online). Chichester, UK: John Wiley & Sons, Ltd; 2017 Mar 6;3(4):CD010973.

70. Altobelli E, Del Negro V, Angeletti PM, Latella G. Low-FODMAP Diet Improves Irritable Bowel Syndrome Symptoms: A Meta-Analysis. Nutrients. 2017 Aug 26;9(9).

71. Newlove Delgado TV, Martin AE, Abbott RA, Bethel A, Thompson Coon J, Whear R, et al. Dietary interventions for recurrent abdominal pain in childhood. Newlove Delgado TV, editor. Cochrane database of systematic reviews (Online). Chichester, UK: John Wiley & Sons, Ltd; 2017 Mar 23;3(4):1–87.

72. Dale HF, Hatlebakk JG, Hovdenak N, Ystad SO, Lied GA. The effect of a controlled gluten challenge in a group of patients with suspected non-coeliac gluten sensitivity: A randomized, double-blind placebo-controlled challenge. Neurogastroenterol Motil. 2018 Mar 15;106:e13332.

73. Gijsbers CFM, Kneepkens CMF, Büller HA. Lactose and fructose malabsorption in children with recurrent abdominal pain: results of double-blinded testing. Acta Paediatrica. 2012 Sep;101(9):e411–5.

74. Abbott RA, Martin AE, Newlove Delgado TV, Bethel A, Thompson Coon J, Whear R, et al. Psychosocial interventions for recurrent abdominal pain in childhood. Cochrane database of systematic reviews (Online). Chichester, UK: John Wiley & Sons, Ltd; 2017 Jan 10;1:CD010971.

75. Bonnert M, Olén O, Lalouni M, Benninga MA, Bottai M, Engelbrektsson J, et al. Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial. Am J Gastroenterol. 2017 Jan;112(1):152–62.

76. Levy RL, Langer SL, van Tilburg MAL, Romano JM, Murphy TB, Walker LS, et al. Brief telephone-delivered cognitive behavioral therapy targeted to parents of children with functional abdominal pain: a randomized controlled trial. Pain. 2017 Apr;158(4):618–28.

77. Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognitive therapy and research. 2012 Oct 1;36(5):427–40.

78. Levy RL, Langer SL, Walker LS, Romano JM, Christie DL, Youssef N, et al. Cognitive-behavioral therapy for children with functional abdominal pain and their parents decreases pain and other symptoms. Am J Gastroenterol [Internet]. 2010 Mar 9;105(4):946–56.

79.   Duarte MAON, Penna FJE, Andrade EENMG, Cancela CSP, Neto JCA, Barbosa TF. Treatment of nonorganic recurrent abdominal pain: cognitive-behavioral family intervention. J Pediatr Gastroenterol Nutr. 2006;43(1):59–64.

80.   Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. J Pediatr Psychol. 2002;30(5):397–408.

81.   Groß M, Warschburger P. Evaluation of a cognitive-behavioral pain management program for children with chronic abdominal pain: a randomized controlled study. Int J Behav Med. Springer US; 2013 Sep;20(3):434–43.

82.   Sanders MR, Shepherd RW, Cleghorn G, Woolford H. The treatment of recurrent abdominal pain in children: A controlled comparison of cognitive-behavioral family intervention and standard pediatric care. J Consult Clin Psychol. 1994;62(2):306–14.

83.   Voort J, Svecova J, Behavioral AJCA, 2010. A retrospective examination of the similarity between clinical practice and manualized treatment for childhood anxiety disorders. The Lancet Psychiatry. 2010;17:322–8.

84.   Jones MC. The elimination of children's fears. Journal of Experimental Psychology. 1924;7:382–90.

85.   Craske MG, Wolitzky-Taylor KB, Labus J, Wu S, Frese M, Mayer EA, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. Behav Res Ther [Internet]. 2011 Jun;49(6-7):413–21.

86.   Kinsinger SW. Cognitive-behavioral therapy for patients with irritable bowel syndrome: current insights. Psychol Res Behav Manag. 2017;10:231–7.

87.   Ljótsson B, Falk L, Vesterlund AW, Hedman E, Lindfors P, Ruck C, et al. Internet-delivered exposure and mindfulness based therapy for irritable bowel syndrome--a randomized controlled trial. Behav Res Ther. 2010 Jun;48(6):531–9.

88.   Viechtbauer W. Conducting Meta-Analyses in R with the metafor Package. Journal of Statistical Software. null; 2010 Aug 1;36(3):1–48.

89.   Ljótsson B, Andersson G, Andersson E, Hedman E, Lindfors P, Andréewitch S, et al. Acceptability, effectiveness, and cost-effectiveness of internet-based exposure treatment for irritable bowel syndrome in a clinical sample: a randomized controlled trial. BMC Gastroenterology 2011 11:1. 2nd ed. 2011 Oct 12;11(1):110.

90.   Ljótsson B, Hesser H, Andersson E, Lackner JM, Alaoui El S, Falk L, et al. Provoking symptoms to relieve symptoms: a randomized controlled dismantling study of exposure therapy in irritable bowel syndrome. Behav Res Ther. 2014 Apr;55:27–39.

91.   Ljótsson B, Hedman E, Andersson E, Hesser H, Lindfors P, Hursti T, et al. Internet-Delivered Exposure-Based Treatment vs. Stress Management for Irritable Bowel Syndrome: A Randomized Trial. Am J Gastroenterol. Nature Publishing Group; 2011 May 3;106(8):1481–91.

92.   Thulin U, Svirsky L, Serlachius E, Andersson G, Ost L-G. The Effect of Parent Involvement in the Treatment of Anxiety Disorders in Children: A Meta-Analysis. Cogn Behav Ther. 2014 Sep;43(3):185–200.

93.   Caes L, Vervoort T, Eccleston C, Vandenhende M, Goubert L. Parental catastrophizing about child's pain and its relationship with activity restriction: the mediating role of parental distress. Pain. 2011 Jan;152(1):212–22.

94.   van der Veek SM, De Haan E, Derkx H, Benninga MA, Boer F. Psychological factors addressed in cognitive behaviour therapy for paediatric functional abdominal pain: Which are most important to target? J Health Psychol. 4 ed. 2017 Feb 1;11(96):1359105317694488.

95.   Vigerland S, Lenhard F, Bonnert M, Lalouni M, Hedman E, Ahlen J, et al. Internet-delivered cognitive behavior therapy for children and adolescents: A systematic review and meta-analysis. Clin Psychol Rev. 2016;50:1–10.

96.   Medieråd S. Ungar & medier 2015: fakta om barns och ungas användning och upplevelser av medier. 2015.

97.   Bonnert M, Ljótsson B, Hedman E, Andersson J, Arnell H, Benninga MA, et al. Internet-delivered cognitive behavior therapy for adolescents with functional gastrointestinal disorders — An open trial. Internet Interventions. Elsevier; 2014 Jul;1(3):141–8.

98.   Hicks CL, Baeyer von CL, McGrath PJ. Online psychological treatment for pediatric recurrent pain: a randomized evaluation. J Pediatr Psychol. Oxford University Press; 2006 Aug;31(7):724–36.

99.   Law EF, Beals Erickson SE, Noel M, Claar R, Palermo TM. Pilot Randomized Controlled Trial of Internet-Delivered Cognitive-Behavioral Treatment for Pediatric Headache. Headache. 2015 Aug 28;55(10):n/a–n/a.

100.   Palermo TM, Wilson AC, Peters M, Lewandowski A, Somhegyi H. Randomized controlled trial of an Internet-delivered family cognitive–behavioral therapy intervention for children and adolescents with chronic pain. Pain. 2009 Nov;146(1-2):205–13.

101.   Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain. 2016 Jan;157(1):174–85.

102.   Trautmann E, (null) BK-H, 2008. Internet-based self-help training for children and adolescents with recurrent headache: a pilot study. Behavioural and Cognitive Psychotherapy. 2008;36:241–5.

103.   Trautmann E, Kröner-Herwig B. A randomized controlled trial of Internet-based self-help training for recurrent headache in childhood and adolescence. Behav Res Ther. 2010 Jan;48(1):28–37.

104.   Voerman JS, Remerie S, Westendorp T, Timman R, Busschbach JJV, Passchier J, et al. Effects of a Guided Internet-Delivered Self-Help Intervention for Adolescents With Chronic Pain. J Pain. 2015 Nov;16(11):1115–26.

105.   Law EF, Groenewald CB, Zhou C, Palermo TM. Impact on Health Care Costs for Adolescents Receiving Adjunctive Internet-Delivered Cognitive-Behavioral Therapy: Results of a Randomized Controlled Trial. J Pain. 2018 Mar 22;:1–28.

106.   Andersson E, Ljotsson B, Smit F, Paxling B, Hedman E, Lindefors N, et al. Cost-effectiveness of internet-based cognitive behavior therapy for Irritable Bowel Syndrome: Results from a randomized controlled trial. BMC public health. 2011;11(1):215.

107.   Lenhard F, Ssegonja R, Andersson E, Feldman I, Ruck C, Mataix-Cols D, et al. Cost-effectiveness of therapist-guided internet-delivered cognitive behaviour therapy for paediatric obsessive-compulsive disorder: results from a randomised controlled trial. BMJ Open. 2017 May;7(5):e015246.

108.   Kling Å, Forster M, Sundell K, Melin L. A randomized controlled effectiveness trial of parent management training with varying degrees of therapist support. Behav Ther. 2010 Dec;41(4):530–42.

109.   Lindberg L, Ulfsdotter M, Jalling C, Skärstrand E, Lalouni M, Lönn Rhodin K, et al. The effects and costs of the universal parent group program - all children in focus: a study protocol for a randomized wait-list controlled trial. BMC public health. 6 ed. 2013;13(1):688.

110.   Vigerland S, Ljótsson B, Thulin U, Ost L-G, Andersson G, Serlachius E. Internet-delivered cognitive behavioural therapy for children with anxiety disorders: A randomised controlled trial. Behav Res Ther. 2016 Jan;76:47–56.

111.   Lenhard F, Andersson E, Mataix-Cols D, Ruck C, Vigerland S, Högström J, et al. Therapist-Guided, Internet-Delivered Cognitive-Behavioral Therapy for Adolescents With Obsessive-Compulsive Disorder: A Randomized Controlled Trial. J Am Acad Child Adolesc Psychiatry. 2017 Jan;56(1):10–2.

112.   Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, et al. Reliability and validity of the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID). J Clin Psychiatry. 2010 Mar;71(3):313–26.

113.   Palermo TM, Law EF, Zhou C, Holley AL, Logan D, Tai G. Trajectories of change during a randomized controlled trial of internet-delivered psychological treatment for adolescent chronic pain: how does change in pain and function relate? Pain. 2015 Apr;156(4):626–34.

114.   Alfvén G, Lindstrom A. A new method for the treatment of recurrent abdominal pain of prolonged negative stress origin. Acta paediatrica (Oslo, Norway : 1992). 2007 Jan;96(1):76–81.