Breaking the vicious circle of fear and avoidance in children with abdominal pain: A mediation analysis

Maria Lalouni a,b,c,*, Hugo Hesser d,e, Marianne Bonnert f,g, Erik Hedman-Lagerlöf h,i, Eva Serlachius b,g, Ola Olén b,c, Brjánn Ljótsson g,h

a Department of Medicine, Karolinska Institutet, Solna, Sweden
b Stockholm Health Care Services, Stockholm County Council, Sweden
c Department of Clinical Neuroscience, Neuro, Karolinska Institutet, Stockholm, Sweden
d Department of Behavioral Sciences and Learning, Linköping University, Sweden
e Center for Health and Medical Psychology, Örebro University, Sweden
f Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden
g Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden
h Department of Clinical Neuroscience, Division of Psychology, Karolinska Institutet, Sweden
i Department of Clinical Neuroscience, Other Center for Integrative Medicine, Karolinska Institutet, Sweden
j Department of Paediatric Gastroenterology and Nutrition, Sachs’ Children’s Hospital, Stockholm, Sweden

A R T I C L E   I N F O
Keywords:
Fear and avoidance
Functional abdominal pain
Internet-CBT
Irritable bowel syndrome
Mediation analysis

A B S T R A C T

Objectives: Exposure-based cognitive behavioral therapy via internet (Internet-CBT) has been shown to reduce symptoms and increase quality of life for children with functional abdominal pain disorders (FAPDs), but the mechanisms of change are unknown. The objective was to examine whether a change in symptom-specific fear and avoidance, i.e., gastrointestinal-specific anxiety (GI-anxiety) and gastrointestinal-specific avoidance (GI-avoidance), mediated changes in parent-reported abdominal symptoms for children receiving Internet-CBT compared with children receiving treatment as usual. A further aim was to assess if baseline levels of the proposed mediators moderated the mediation.

Methods: Weekly assessments of child-reported mediators and parent-reported outcome from 90 children aged 8–12 who were included in a randomized controlled trial were used in univariate and multivariate growth models to test the direct effect of treatment on outcome and the indirect effects via mediators and moderated mediation.

Results: Treatment condition significantly predicted the slope of the mediators (a-path), in favor of Internet-CBT, and mediators were correlated with the outcome (b-path). The indirect effects of the mediators on the outcome (cross-product of the a and b-paths) were significantly different from zero for both GI-avoidance, ab = 1.43, 95% CI [0.42, 3.23]; and GI-anxiety ab = 1.58, 95% CI [0.43, 3.62]. Baseline levels of the proposed mediators moderated the size of the mediation.

Conclusions: GI-anxiety and GI-avoidance were mediators of change in Internet-CBT and high levels of the mediators at baseline were associated with larger mediated effects. Healthcare professionals should be aware of, and inform families about, the potential benefits of reducing symptom-specific fear and avoidance.

1. Introduction

Pediatric functional abdominal pain disorders (FAPDs) are characterized by medically unexplained abdominal pain and other abdominal symptoms [1]. FAPDs are associated with internalizing symptoms, e.g., anxiety [2] and low quality of life [3]. The disorders are prevalent (13.5%) [4] and for about 40% of the children the symptoms remain into adulthood [5]. This chronicity may partly be explained by the fear and avoidance model, in which an individual who perceives pain as a threat reacts with avoidance [6,7]. Avoidance of acute pain has an evolutionary advantage as damage to the individual is minimized, but when the pain becomes chronic, avoidance maintains functional disability and

* Corresponding author at: Department of Clinical Neuroscience, Karolinska Institutet, Nobels väg 7, 17177 Stockholm, Sweden.
E-mail address: maria.lalouni@ki.se (M. Lalouni).
https://doi.org/10.1016/j.jpsychores.2020.110287
Received 12 May 2020; Received in revised form 29 October 2020; Accepted 31 October 2020
Available online 4 November 2020
0022-3999/© 2020 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).
symptom severity [6].

While the empirical support for pharmacological and dietary interventions is weak for pediatric FAPDs [8,9], studies of cognitive behavioral therapy (CBT) have shown promising results [10–12]. Multiple components are typically used in CBT, such as cognitive restructuring of maladaptive thoughts, exposure exercises, relaxation, and parent management techniques. However, it is largely unknown which treatment components are effective, through which mechanisms they work, and for whom CBT is effective.

Our research group have shown that exposure-based CBT is effective in reducing abdominal symptoms in adults, adolescents and children with FAPDs [11–13]. In exposure-based CBT for FAPDs, the patients gradually expose themselves to symptom-provoking stimuli (such as eating pizza) and approach situations in which symptoms are perceived as intolerable (such as being in school). This approach is hypothesized to decrease fear and avoidance related to symptoms and thereby enables symptom reduction. Exposure-based CBT addresses the patient’s maladaptive behavioral, cognitive and emotional reactions to the symptoms, as has been suggested to be the most important target in psychological treatments for FAPDs [14]. Exposure exercises represent an activating and patient-involving treatment, as has been recommended in a recent review of the management of functional somatic syndromes [15].

An important aim of mediation analyses is to uncover mechanisms of change and to use such knowledge to maximize treatment outcomes. Mediation analyses use statistical methods to assess whether all or some of the treatment effect works indirectly via a mediator, referred to as the mediated or indirect effect [16]. When a treatment is compared with a control, mediation can be confirmed if (1) the treatment changes the mediator and if (2) the change in the mediator is correlated with the outcome.

A moderator is a variable that affects the strength of the association between two variables. Moderation can be combined with mediation to test for whom, or under what conditions, the mediational processes operate. Moderated mediation can thus reveal for which patients the best of our knowledge, the first study to assess whether a reduction in GI-gastrointestinal-specific avoidance (GI-avoidance) mediated the symptom improvement for children with FAPDs receiving Internet-CBT or treatment as usual, with sustained improvements at a 36-week follow-up [12]. The aim of the present study was to investigate whether gastrointestinal-specific anxiety (GI-anxiety) and gastrointestinal-specific avoidance (GI-avoidance) mediated the symptom improvement for children with FAPDs receiving Internet-CBT compared with children receiving treatment as usual. A further aim was to assess if high levels of the mediators at baseline moderated the mediation. We hypothesized that GI-anxiety and GI-avoidance would be mediators of change and that children with high baseline levels of the proposed mediators would have a larger mediated effect. This is, to the best of our knowledge, the first study to assess whether a reduction in GI-specific fear and avoidance mediate symptom improvement in pediatric FAPDs.

2. Methods

2.1. Design

This study was based on data from a randomized controlled trial [12] registered in Clinicaltrials.gov in August 2016 (NCT02873078) and approved by the Regional Ethical Board in Stockholm, Sweden in August 2016 (2016/1289–31).

2.2. Recruitment and inclusion criteria

Physicians, who had been informed about the study via emails, visits to clinics and lectures, referred all participants to the study between September 2016 and April 2017. All referred children were regular patients at the physicians’ clinics. The study was conducted at the Child and Adolescent Psychiatry Research Centre in Stockholm. Inclusion and exclusion criteria were assessed and informed consent was obtained from parents and children during the initial clinical assessment at the research clinic. Ninety children and their parents were randomized to either Internet-CBT or treatment as usual. Inclusion criteria were: (a) age ≥ 8 and ≤ 12 years, (b) at least one of following functional abdominal pain disorders according to the ROME IV criteria: irritable bowel syndrome, functional dyspepsia, or functional abdominal pain not otherwise specified [1], (c) stable dose at least one month if using psychopharmacological medications, (d) internet access, and (e) basic reading and writing skills (child and one parent). Children were excluded if they had (f) another somatic disease that explained their abdominal symptoms, (g) psychiatric or social problems that needed immediate care, including school absenteeism >40%, or (h) another ongoing psychological treatment.

2.3. Randomisation

Patients and their parents were consecutively randomized to Internet-CBT or treatment as usual in blocks with different sizes (5–19) by an independent researcher using www.random.org. Randomization was conducted on a 1:1 ratio (balanced within the blocks) resulting in 46 children in Internet-CBT and 44 children in treatment as usual.

2.4. Interventions

2.4.1. Internet-CBT

Internet-CBT consisted of 10 weekly modules for children and 10 weekly modules for parents. The children and parents completed a mean of 9.3 and 9.2 out of 10 weekly modules, respectively. Therapist support was provided via written text messages within the online treatment platform. Short texts, images and films used were used to illustrate principles of the treatment. The treatment included an explanatory model of how abdominal pain can be maintained by GI-anxiety and GI-avoidance (Fig. 1).

The exposure-based approach was presented as a means to break the vicious circle of fear and avoidance, and the families were taught that exposure exercises could help the children take control of their lives. In the children’s modules, children mapped their behaviors related to GI-avoidance, such as avoiding foods or situations in which they feared having symptoms. The children and parents made a hierarchy of exposure exercises based on this mapping and set their own behavioral goals for the treatment. The children themselves chose from the hierarchy which exposure exercises to engage in during the coming week. Examples of exposure exercises were to eat symptom-provoking food or to play with friends when having abdominal symptoms. An example of a goal was to go to school every day despite abdominal symptoms. A short mindfulness exercise was used to help children engage in the challenging exposure exercises without distracting themselves from the abdominal symptoms. Children in Internet-CBT were allowed to participate in other treatments, but were encouraged to decrease...
abdominal medications, in order to regain natural control of bowel habits and increase exposure to symptoms.

The main focus of the parents’ modules was to encourage and facilitate their child’s work with the exposure exercises. Another important aspect was to help the parents decrease their attention to their child’s abdominal symptoms, which is in accordance with the exposure-based approach. Parents were taught to first briefly validate the child’s pain experience and then help their child shift focus. Parents were also instructed to plan for joyful activities with their child without focusing on abdominal symptoms. A comprehensive description of the Internet-CBT protocol is available elsewhere [23].

2.4.2. Treatment as usual
In treatment as usual, patients and parents were informed that they would be offered Internet-CBT after 10 weeks. During this time, they were allowed to continue with any current treatment and seek any further help that they deemed necessary. Treatments included visits to health care professionals, medications, and dietary interventions, reported in detail in the article of the randomized controlled trial [12].

2.5. Measures

2.5.1. Outcome variable

The outcome variable was the PedsQL Gastrointestinal symptoms scale (PedQL). The PedQL consists of 9 items assessing abdominal symptoms (abdominal pain, diarrhea, constipation, nausea, vomiting, abdominal discomfort, passing gas, not feeling hungry, and bloating) that are rated on a 5-point scale ranging from never (0) to almost always (4). It is specifically developed to fit children with FAPDs and has an acceptable internal consistency (Cronbach’s alpha 0.77) [24]. The PedQL is transformed to a reversely scored 0–100 scale, with higher values indicating milder symptoms. In this study, we used parental assessments of the outcome variable. Parents’ reports of the PedQL were in line with the children’s reports, but showed larger effects and were therefore chosen to maximize power [12]. However, children’s assessments of the PedQL were also analyzed as an outcome variable. These results are presented in Appendix C.

2.5.2. Proposed mediators

GI-avoidance (BRQ-C) was assessed with a child-adapted and shortened version of the Irritable Bowel Syndrome Behavioral Responses Questionnaire [25]. The BRQ-C comprises 11 items and the total score range from 11 to 77. It includes items like “I avoid exercise when I have stomach pains” and “I avoid certain foods when I have bowel problems”. GI-anxiety (VSI-C) was assessed with a child-adapted and shortened version of the Visceral Sensitivity Index [26]. The VSI-C comprises 7 items and the total score ranges from 0 to 35 with items like “I often worry about problems in my belly” and “When I feel discomfort in my belly, it frightens me”. Both the proposed mediators were child-rated. The adaptations of the original scales were made to adjust the scales to a child-population with different kinds of FAPDs, as they were originally developed for adults with irritable bowel syndrome. Further, there was a need to shorten the scales to enable repeated measurements without overloading the children with questions. The adaptations and validations of the BRQ-C and the VSI-C are described in detail in a separate article (in manuscript) and a brief description is provided in the Appendix A.

2.5.3. Time points of assessment

Abdominal symptoms were assessed weekly by the parents (and the children) during the treatment (week 1–10). At baseline and follow-up (weeks 0 and 11), another version of the PedQL that has a one-month recall period instead of one week was used. Because the mediation analysis was based on weekly assessments, the 0 and 11 week PedQL assessments were not included in the analysis. GI-anxiety and GI-avoidance were assessed bi-weekly by the children (with a one-week
The primary analytic models used to test direct and indirect effects (mediation, moderated mediation) were univariate and multivariate growth models with random effects [28, 29]. The mediators of interest were child-assessed GI-anxiety and GI-avoidance and the outcome was parent-assessed abdominal symptoms. We also performed the analyses with child-assessed abdominal symptoms as the outcome, reported in Appendix B. Models were fitted using Mplus Version 7.4 and incorporated all available data [30]. Effect sizes in the form of standardized mean differences (Cohen’s d) were computed based on estimated means at the endpoint [31]. Univariate growth models were combined into a multivariate parallel process growth model to test for mediation following the recommendations provided by Cheong, MacKinnon and Khoo [32]. The parallel process growth model was subsequently extended to moderated mediation by including the baseline scores of the mediator variable as a moderator of the effect of treatment on the mediator [33]. Mediation was formally evaluated by a bootstrapped 95% confidence interval method both when testing GI-avoidance (BRQ-C) and GI-anxiety (VSI-C). The ab-product was statistically significant (i.e., did not include zero) as evaluated with the bootstrapped confidence interval method both when testing GI-avoidance (BRQ-C) \( ab = 1.43, 95\% \text{ CI } [0.42, 3.23] \) and GI-anxiety (VSI-C) \( ab = 1.58, 95\% \text{ CI } [0.43, 3.62] \) as mediators. The proportion mediated effect for the mediators was 79.8% for BRQ-C and 78.6% for VSI-C. Mediation analyses based on the child-rated outcome showed similar results, see Appendix C.

3.2. Moderated mediation

The estimate of moderated mediation was statistically significant for GI-avoidance (BRQ-C) \( \text{mod-ab} = 0.16, 95\% \text{ CI } [0.05, 0.36] \) and GI-anxiety (VSI-C) \( \text{mod-ab} = 0.15, 95\% \text{ CI } [0.04, 0.44] \). Figs. 3 and 4 illustrate the mediated effects as a function of the moderators (baseline values on the mediators) [33]. As shown in Figs. 3 and 4, the mediated effects of GI-avoidance (BRQ-C) and GI-anxiety (VSI-C) on abdominal symptoms (PedQL) increased with higher baseline scores on the mediators. For children scoring low on the mediators at baseline (1 SD below the grand mean), the mediated effect was small and not statistically significant different from zero, whereas as for those with a high baseline scores on the mediators (1 SD above the grand mean) the mediated effect was statistically significant and large (Figs. 3 and 4). Moderated mediation analyses based on the child-rated outcome showed similar results, see Appendix C.

3.1. Mediation analysis

The main results from parallel the process growth models are shown in Fig. 2. Condition significantly predicted the slope of the mediator in favor of Internet-CBT (a-path) and the slope of the mediator was significantly correlated with the slope of the outcome (b-path) for GI-avoidance (BRQ-C) and GI-anxiety (VSI-C). The ab-product was statistically significant (i.e., did not include zero) as evaluated with the bootstrapped confidence interval method both when testing GI-avoidance (BRQ-C) \( ab = 1.43, 95\% \text{ CI } [0.42, 3.23] \) and GI-anxiety (VSI-C) \( ab = 1.58, 95\% \text{ CI } [0.43, 3.62] \) as mediators. The statistical analyses are described in detail in Appendix B.

The main results from parallel the process growth models are shown in Fig. 2. Condition significantly predicted the slope of the mediator in favor of Internet-CBT (a-path) and the slope of the mediator was significantly correlated with the slope of the outcome (b-path) for GI-avoidance (BRQ-C) and GI-anxiety (VSI-C). The ab-product was statistically significant (i.e., did not include zero) as evaluated with the bootstrapped confidence interval method both when testing GI-avoidance (BRQ-C) \( ab = 1.43, 95\% \text{ CI } [0.42, 3.23] \) and GI-anxiety (VSI-C) \( ab = 1.58, 95\% \text{ CI } [0.43, 3.62] \) as mediators. The proportion mediated effect for the mediators was 79.8% for BRQ-C and 78.6% for VSI-C. Mediation analyses based on the child-rated outcome showed similar results, see Appendix C.

2.6. Statistical analysis

The primary analytic models used to test direct and indirect effects (mediation, moderated mediation) were univariate and multivariate growth models with random effects [28, 29]. The mediators of interest were child-assessed GI-anxiety and GI-avoidance and the outcome was parent-assessed abdominal symptoms. We also performed the analyses with child-assessed abdominal symptoms as the outcome, reported in Appendix B. Models were fitted using Mplus Version 7.4 and incorporated all available data [30]. Effect sizes in the form of standardized mean differences (Cohen’s d) were computed based on estimated means at the endpoint [31]. Univariate growth models were combined into a multivariate parallel process growth model to test for mediation following the recommendations provided by Cheong, MacKinnon and Khoo [32]. The parallel process growth model was subsequently extended to moderated mediation by including the baseline scores of the mediator variable as a moderator of the effect of treatment on the mediator [33]. Mediation was formally evaluated by a bootstrapped 95% confidence interval method both when testing GI-avoidance (BRQ-C) \( ab = 1.43, 95\% \text{ CI } [0.42, 3.23] \) and GI-anxiety (VSI-C) \( ab = 1.58, 95\% \text{ CI } [0.43, 3.62] \) as mediators. The proportion mediated effect for the mediators was 79.8% for BRQ-C and 78.6% for VSI-C. Mediation analyses based on the child-rated outcome showed similar results, see Appendix C.

2.5. Results

There were 90 children (69% girls) with an average age of 10.2 (SD = 1.4) years included in the study. For each child one parent was included, of which 86% were mothers. The proportion missing data in the entire sample was 6.5%. This did not include the planned missing data of the proposed mediators, which according to the design was 50% on weeks 1–10 leaving a maximum of 45 participants each week instead of 90. Table 1 presents descriptive statistics for the outcome measure and the proposed mediators for both conditions.

Univariate growth models revealed statistically significant differences in average trajectories on the primary outcome parent ratings of abdominal symptoms (PedQL) favoring Internet-CBT relative to treatment as usual: \( \text{estimate} = 1.71, \text{SE} = 0.83, P = 0.04 \), Cohen’s \( d = 0.65 \). There was also a statistically significant difference between conditions on the proposed mediators GI-avoidance (BRQ-C) and GI-anxiety (VSI-C) favoring Internet-CBT over treatment as usual: \( \text{estimate} = -2.28, \text{SE} = 0.67, P = 0.001 \), Cohen’s \( d = 0.48 \); \( \text{estimate} = -1.54, \text{SE} = 0.50, P = 0.002 \), Cohen’s \( d = 0.35 \). In all univariate growth models, there was a significant unexplained heterogeneity in individual growth trajectories after adjusting for treatment effects (all \( P < 0.01 \)). This made it possible to evaluate mediation using parallel process growth models.

Table 1

| Time point | PedQL (parent report) | BRQ-C (child report) | VSI-C (child report) |
|------------|-----------------------|----------------------|----------------------|
|            | n M SD                | n M SD               | n M SD               |
| 0          | - - -                 | 90 31.9 13.4         | 90 14.4 7.9          |
| 1          | 89 66.4 14.7          | 45 28.8 9.9          | 45 11.3 7.8          |
| 2          | 86 69.8 13.0          | 45 26.7 11.7         | 45 10.6 7.7          |
| 3          | 86 69.3 12.9          | 45 26.3 13.1         | 45 9.8 7.1           |
| 4          | 85 72.0 14.1          | 45 24.6 9.5          | 45 10.0 7.3          |
| 5          | 88 71.2 15.4          | 43 24.2 12.0         | 45 8.8 6.7           |
| 6          | 81 72.1 15.5          | 45 25.0 12.4         | 42 9.2 7.9           |
| 7          | 84 72.9 14.9          | 43 22.7 11.5         | 45 8.0 6.2           |
| 8          | 78 72.9 15.1          | 45 23.6 12.1         | 40 7.6 7.5           |
| 9          | 82 73.4 16.3          | 40 21.6 13.1         | 45 8.0 6.2           |
| 10         | 83 75.0 16.1          | 40 22.1 10.5         | 39 8.5 8.5           |
| 11         | - - -                 | 86 20.5 10.3         | 85 7.2 6.4           |
| Total obs  | 842 612               | 611                  |                      |
| Missing obs| 58 18                 | 19                   |                      |

PedQL, PedsQL Gastrointestinal Symptom Scale measuring abdominal symptoms; BRQ-C, Behavioral Responses Questionnaire Child-adapted version, measuring gastrointestinal-specific avoidance behaviors; VSI-C, Visceral Sensitivity Index Child-adapted version, measuring gastrointestinal-specific anxiety; n, Number of observations; M, Mean; SD, Standard deviation; Total obs, total number of observations; Missing obs, number of unplanned missing observations.
4. Discussion

The aim of this study was to assess if a reduction in symptom-specific fear and avoidance would mediate symptom change for children with FAPDs receiving exposure-based Internet-CBT compared with treatment as usual. We used data from a randomized controlled trial including 90 children aged 8–12 with FAPDs. In line with our hypotheses, we observed that a decrease in children’s GI-anxiety and GI-avoidance mediated the improvement in parent-reported abdominal symptoms for children receiving Internet-CBT compared with children receiving treatment as usual. Further analyses showed that for children in Internet-CBT, higher baseline scores on the proposed mediators were associated with stronger mediated effects. The results of this study can be interpreted in the light of the fear and avoidance model [35]. According to this model fear of symptoms and avoidance of activities that may elicit symptoms will increase symptom severity and disability, while approaching symptoms and feared situations leads to decreased symptoms. Approaching feared situations and provoking symptoms is the key element of exposure-based CBT and the results of this mediation analysis corroborate the hypothesized mechanism of change: by breaking the vicious circle of fear and avoidance the symptoms decreases and function and quality of life increases.

Previous studies have shown that reductions in GI-anxiety and GI-avoidance mediate symptom improvement in adults and that GI-avoidance mediate symptom improvement in adolescents during exposure-based cognitive behavioral therapy for irritable bowel syndrome [18,19]. The adult study also demonstrated that the mediated effect of GI-avoidance was more pronounced for patients with high values of GI-avoidance at baseline [18]. This study confirms these results and expands them to young children with a broader range of FAPDs. The moderated mediation shows that the indirect effect of the mediators on outcome seen in Internet-CBT is more pronounced for children with higher baseline values of the proposed mediators, which gives further support to GI-anxiety and GI-avoidance as key mediators in Internet-CBT for children with FAPDs. The moderated mediation also indicates that Internet-CBT may be particularly beneficial for children high in symptom-specific fear and avoidance.

Future mediation studies should assess if parental responses to children’s symptoms affect the children’s symptoms, avoidance behaviors, and fear of symptoms. Further, it would be interesting if mediators

---

**Fig. 2.** Mediation models for GI-avoidance and GI-anxiety and the treatment outcome model without the mediator. The a-paths show the treatment effect on the mediator’s growth trajectory. The b-paths show how the participants’ individual changes on the mediator correlate with the individual changes of the outcome trajectory. The c-paths show the remaining effects for treatment on outcome when controlling for the mediated effect. The c-path shows the treatment effect for Internet-CBT vs treatment as usual on the outcome trajectory. *P < 0.05; **P < 0.01.

**Fig. 3.** A visual representation of the conditional indirect effect on abdominal symptoms (PedQL) via the mediator GI-avoidance (BRQ-C) as function of baseline values on the mediator (range: 1 SD +/− grand mean), with bootstrapped confidence interval (CI) bands. The shaded area represents an indirect effect that is zero. The vertical line represents the boundary of the region of significance.
that have been assessed in other studies of pediatric FAPDs, such as pain reactivity and coping strategies [20,21], were compared to the mediators found in this study. Another recommendation for future studies is to include experimental manipulation of potential mediators, to be able to meticulously investigate mechanisms of change.

4.1. Strengths and limitations

Strengths of the study include the randomized study design as well as the use of multiple assessment points during the course of treatment for both proposed mediators and outcome. The mediation analyses were performed using parallel process growth models that assess changes in both mediators and outcome at the individual level, which is generally a preferred approach for testing longitudinal mediation [32]. Another strength of the study is the use of the two theoretically relevant and distinct mediators: GI-anxiety and GI-avoidance. A limitation of the study is that temporal order was not established between mediators and outcome. Other limitations are the fact that potential confounding in the b-path (affecting both mediator and outcome) is not handled by the randomization and that the sample size was in the lower acceptable range for the models. The use of the parent-reported measure of abdominal symptoms as outcome in the mediation analysis instead of the child-reported measure is a limitation. The decision to use the parent-reported outcome was made to maximize the statistical power of the mediation analysis. The effect size of the parent report of their child’s abdominal symptoms was larger than for the child-reported abdominal symptoms, as described in the main outcome study [12]. Thus, using the parent-rated measure as the outcome reduced the risk for making a Type II-error. However, we also performed the mediation and moderated mediation analyses based on the child-reported measure and report these in Appendix C. The results from these analyses were in line with the primary analysis. Another limitation is that the treatment as usual comparison group did not control for attention or expectation during Internet-CBT. Also, it is important to note that the high percentages of the effect explained by the mediators (79.8% for BRQ-C and 78.6% for VSI-C) should be interpreted with caution because of the small sample size as the effect is regarded as unstable in sample sizes below 500 [35].

5. Conclusion

This is the first mediation study of exposure-based CBT in FAPDs to clearly demonstrate both mediation and moderated mediation of symptom-specific fear and avoidance. The results show that GI-anxiety and GI-avoidance are mediators of change for children with FAPDs in exposure-based Internet-CBT compared with treatment as usual. Children with high baseline values of GI-anxiety and GI-avoidance likely benefit more from exposure-based Internet-CBT than children with low symptom-specific fear and avoidance.

Financial support

This study was supported by grants from the Jane and Dan Olsson Foundation (4-1559/2013), the Swedish Research Council (521-2013-2846), the Kempe-Carlgrenska Foundation, the Ruth and Richard Julin Foundation (2012Juli0048), the Majblomman Foundation, the Ishizu Matsumurai’s Donation, the Bengt Ihre Foundation (SLS-331861), the Bengt Ihre research fellowship in Gastroenterology, the Swedish Society of Medicine (SLS331681, SLS-410501), Swedish Research Council for Health, Working life, and Welfare (2014-4052), and Centre for Psychiatry Research. Financial support was also provided through the regional agreement on medical training and clinical research between Stockholm County Council and Karolinska Instutet (20130129 and 20150414). None of the funding bodies had any influence on study design, execution or publication of the study.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Declaration of Competing Interest

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare that they have no competing interests.
Acknowledgements

The authors would like to thank Gabriella Carpelan and Livia van Leuven for their administrative support during the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychores.2020.110287.

References

[1] J.S. Hyams, C. Di Lorenzo, M. Saps, R.J. Shulman, A. Staiano, M. van Tilburg, Functional disorders: children and adolescents, Gastroenterology 150 (2016) 1456–1468, https://doi.org/10.1053/j.gastro.2016.02.015.
[2] I.E. Schulte, F. Petermann, M. Noeker, Functional abdominal pain in childhood: from etiology to maladaptation, Psychother. Psychosom. 79 (2010) 73–86, https://doi.org/10.1159/000270915.
[3] J.W. Varni, C.B. Bendo, S. Nurko, R.J. Shulman, M.M. Self, J.P. Francisci, et al., Health-related quality of life in pediatric patients with functional and organic gastrointestinal diseases, J. Pediatr. 166 (2015) 85–90, https://doi.org/10.1016/j.jpeds.2014.08.022.
[4] J.J. Korterink, K. Diederen, M.A. Benninga, M.M. Tabbers, Epidemiology of functional pediatric abdominal pain disorders: a meta-analysis, PLoS One 10 (2015), e0136992, https://doi.org/10.1371/journal.pone.0136992.
[5] S. Horst, G. Shelby, J. Anderson, S. Acra, D.B. Polk, B.R. Saville, et al., Predicting Functional disorders: children and adolescents, Gastroenterology 150 (2016) 890–900, https://doi.org/10.1053/j.gastro.2016.02.016.
[6] P. Browne, S.C.J. Nagelkerke, F.S. van Etten-Jamaludin, M.A. Benninga, M. Tabbers, Pharmacological treatments for functional nausea and functional dyspepsia in children: a systematic review, Expert. Rev. Clin. Pharmacol. 11 (2018) 1195–1208, https://doi.org/10.1080/17512433.2018.1540298.
[7] R.A. Abbott, A.E. Martin, T.V. Newlove-Delgado, A. Bethel, R.S. Wheat, J. Thompson Coon, et al., Internet-delivered cognitive behavior therapy for children with pain-related functional gastrointestinal disorders: feasibility study, JMIR Ment. Health. 4 (2017), e32, https://doi.org/10.2196/menthl.7985.
[8] R.L. Levy, S.L. Langer, J.M. Romano, J. Labus, L.S. Walker, T.B. Murphy, et al., Cognitive mediators of treatment outcomes in pediatric functional abdominal pain, J. Clin. Pain 30 (2014) 1033–1043, https://doi.org/10.1097/AJP.0000000000000077.
[9] M. Bonnert, O. Olén, J. Bjureberg, M. Lalouni, E. Hedman-Lagerlöf, E. Serlachius, et al., The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: a mediation analysis, Behav. Res. Ther. 105 (2018) 27–35, https://doi.org/10.1016/j.brat.2018.03.006.
[10] M. Lalouni, O. Olén, J. Bjureberg, M. Lalouni, E. Hedman-Lagerlöf, E. Serlachius, et al., The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: a mediation analysis, Behav. Res. Ther. 105 (2018) 27–35, https://doi.org/10.1016/j.brat.2018.03.006.
[11] M. Bonnert, O. Olén, J. Bjureberg, M. Lalouni, E. Hedman-Lagerlöf, E. Serlachius, et al., The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: a mediation analysis, Behav. Res. Ther. 105 (2018) 27–35, https://doi.org/10.1016/j.brat.2018.03.006.
[12] M. Bonnert, O. Olén, J. Bjureberg, M. Lalouni, E. Hedman-Lagerlöf, E. Serlachius, et al., The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: a mediation analysis, Behav. Res. Ther. 105 (2018) 27–35, https://doi.org/10.1016/j.brat.2018.03.006.
[13] R.K. Wickell, G.L. Olsson, S.C. Hayes, Mediators of change in acceptance and commitment therapy for pediatric chronic pain, Pain 152 (2011) 2792–2801, https://doi.org/10.1016/j.pain.2011.09.003.
[14] P. Henningsen, S. Zipfel, H. Sattel, F. Creed, Management of Functional Somatic Syndromes and Bodily Distress, Psychother. Psychosom. 87 (2018) 12–31, https://doi.org/10.1055/s-0044484143.
[15] R.M. Baron, D.A. Kenny, The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, J. Pers. Soc. Psychol. 51 (1986) 1173–1182.
[16] P.D. Browne, S.C.J. Nagelkerke, F.S. van Etten-Jamaludin, M.A. Benninga, M. Tabbers, Pharmacological treatments for functional nausea and functional dyspepsia in children: a systematic review, Expert. Rev. Clin. Pharmacol. 11 (2018) 1195–1208, https://doi.org/10.1080/17512433.2018.1540298.
[17] M. Bonnert, O. Olén, J. Bjureberg, M. Lalouni, E. Hedman-Lagerlöf, E. Serlachius, et al., The role of avoidance behavior in the treatment of adolescents with irritable bowel syndrome: a mediation analysis, Behav. Res. Ther. 105 (2018) 27–35, https://doi.org/10.1016/j.brat.2018.03.006.
[18] H. Hesser, E. Hedman-Lagerlöf, E. Andersson, P. Lindfors, B. Ljostsson, 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. 86 (2018) 254–267, https://doi.org/10.1037/cpp0000273.
[19] R.M. Baron, D.A. Kenny, The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, J. Pers. Soc. Psychol. 51 (1986) 1173–1182.
[20] A.A. Morgan-Lopez, D.P. MacKinnon, Demonstration and evaluation of a method for assessing mediated moderation, Behav. Res. Methods 38 (2006) 77–87.
[21] P. Henningsen, S. Zipfel, H. Sattel, F. Creed, Management of Functional Somatic Syndromes and Bodily Distress, Psychother. Psychosom. 87 (2018) 12–31, https://doi.org/10.1055/s-0044484143.
[22] H. Hesser, E. Hedman-Lagerlöf, E. Andersson, P. Lindfors, B. Ljostsson, 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. 86 (2018) 254–267, https://doi.org/10.1037/cpp0000273.
[23] R.M. Baron, D.A. Kenny, The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations, J. Pers. Soc. Psychol. 51 (1986) 1173–1182.
[24] A.A. Morgan-Lopez, D.P. MacKinnon, Demonstration and evaluation of a method for assessing mediated moderation, Behav. Res. Methods 38 (2006) 77–87.